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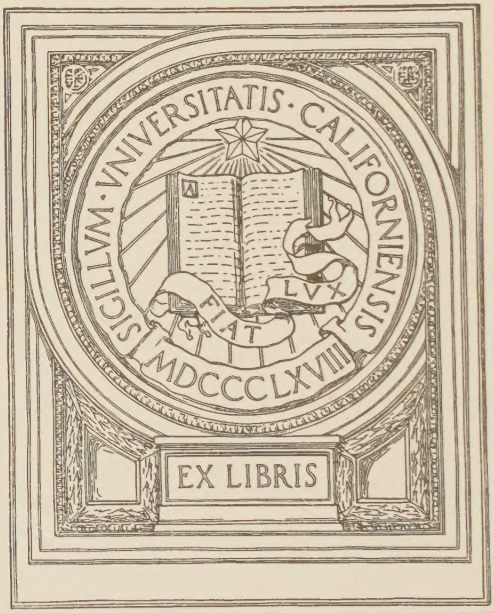

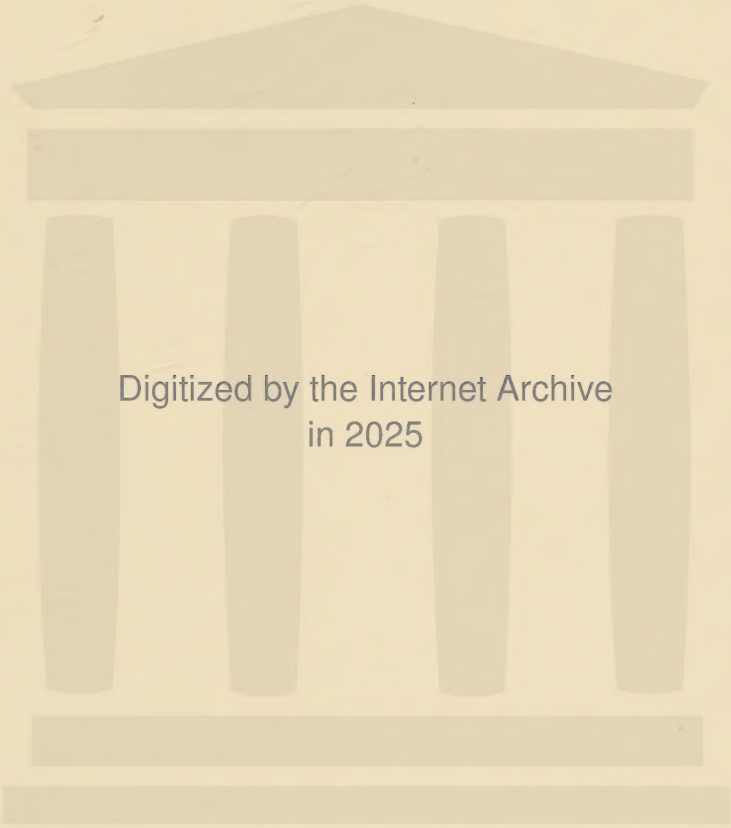
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CHRONICALLY IMPLANTED CARDIOVASCULAR INSTRUMENTATION

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National Symposium on

CHRONICALLY IMPLANTED CARDIOVASCULAR INSTRUMENTATION

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PREFACE

Onrushing future shock may be the cause, but many of us experience attacks of an atavistic urge for the past styles of scientific reporting, when descriptions of new findings were coupled with anecdotal, personalized insights into the investigator's conceptual and technical difficulties and his approaches to solving them. The literary overpopulation problem, among other reasons, has necessitated pruning virtually all such peregrinations from current reports. Certainly a necessary economy, but an ill-defined sense of sterility is an inevitable result.

This sensation is particularly acute when the study design utilizes chronically instrumented animals. Many of the technical details provide the difference between success and failure in this difficult trade, but because of their subtlety, such considerations are not easily summarized in research reports.

As an aid in bridging the communications gap, a symposium was convened at the University of Kentucky on October 17-20, 1971, to record some of these details before they vanished. The papers collected in this volume are the outgrowth of that symposium and record the current status of available techniques as a benchmark for measurement of future progress. Not all of the contributions are strictly "scientific" in the currently accepted definition of the term, but they are exceedingly important for conveying the flavor of scientific studies conducted in the chronically prepared animal, and for helping the novice over the hurdles.

Grateful appreciation is due a number of people who made this publication possible. Dr. Ward Griffen, Professor and Chairman of the Department of Surgery of the University of Kentucky Medical Center, has participated actively in this project, and his contributions were essential to its successful completion. Dr. Harvey Savely and Dr. William Wisecup of the Air Force Office of Scientific Research (AFSC) provided essential support and encouragement. Dr. Joseph C. Greenfield, Jr., Dr. H. Lowell Stone, and Dr. Francis L. Abel shared the editorial and coordinating tasks. Mrs. Jean Fischer, Mrs. Carolyn Wright, Mrs. Suzanne Osborne, and the staff of the Wenner-Gren Research Laboratory handled the many secretarial and administrative details. Mr. Cecil Woolfolk and Mr. Robert Stanifer have been responsible for implementing many of the techniques in our own laboratory,

and Ms. Joyce Evans has held the whole thing together. The final typescript was prepared by Mr. John W. Barker and his associates in the University of Kentucky Printing Department, and we are indebted to Academic Press for their advice and cooperation.

Ernest P. McCutcheon

CHRONICALLY IMPLANTED CARDIOVASCULAR INSTRUMENTATION

1

INTRODUCTION

1. INTRODUCTION. THE SIGNIFICANCE OF CHRONICALLY IMPLANTED INSTRUMENTATION.[1]

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VALIDITY OF THE CHRONIC ANIMAL PREPARATION

The chronic animal preparation is one of the most important components of a rapidly expanding technological base supporting innovative research in the biological sciences. The importance of this methodology stems from its usefulness for exploring new concepts of biological function, especially the regulation of interacting system components. The chronically prepared animal is also a vital link in the development of non-invasive evaluation of many characteristics of biological systems, since it provides a standard for verification of new measurement techniques. Because this type of experimental preparation has reached an advanced level in cardiovascular applications, a review of the current status of the procedures and instrumentation used in circulatory studies is appropriate. This book is the first attempt to consolidate information of this type.

Before introducing the specific concerns addressed in this book, a brief summary of some of the evidence establishing the validity of this experimental approach is warranted. Considerable support for use of the chronically instrumented animal has now accumulated in the physiological literature.

The advancement of physiological understanding depends on results of experiments utilizing a wide spectrum of design principles. The acute, anesthetized preparation is one classic model, with the basic appeal of enhanced capability for separation and isolation of system components and for manipulation of individual variables. Implicit in this design is the assumption that the effects of anesthesia, if not a minor influence, are at least fully understood. However, the changes produced by anesthetic agents are

[1] Supported, in part, by USAF/OSR (AFSC) Contract No. F44620-69-C-0127.

profound and extensive; death inevitably results with sufficient prolongation of the depth of anesthesia usually required for complex acute experiments. Furthermore, the pharmacologic effects are not only far from minor, but are poorly understood, as witnessed by the continuous output of research studies of the responses to these drugs (1-7).

Additional alterations are produced when the effects of surgery are added to those of anesthesia. For example, as demonstrated so clearly by Rushmer (8), marked cardiovascular changes occur with thoracotomy. Simply opening the chest produces a decrease in heart size to its minimal volume, and Gauer and Henry (9) described subendocardial hemorrhages caused by ventricular contraction with inadequate residual volume. The problems are increased when the surgery is extensive. For instance, the isolated heart preparation does not generate normal pressure or stroke volume and frequently can be maintained only with continous catecholamine infusion (3, 10, 11).

The development of new, testable concepts is the essence of research, for the removal of conceptual blocks to progress is often of greater importance than acquisition of new but disorganized facts. While the study of bacteria can lead to important concepts of great value in understanding functional characteristics of higher organisms, such concepts are extremely tentative until tested and verified for the particular system under examination. As so aptly stated by Rushmer, "Experimental data are applicable *without reservation* only to the specific conditions under which they were collected" (12). When the subject of physiological study is an integral component of a system, but the experiment is limited to a simplified, isolated segment, hazards in use of the results for development of new concepts are added to the functional limitations noted above. Again the cardiovascular system provides an appropriate illustration. The force-velocity-length concept defines the function of isolated papillary muscle, but it cannot be applied for rigorous analysis of the properties of the intact heart (13).

The pioneering work of Van Citters, Franklin, and Hawthorne, in addition to that of Rushmer, brought widespread recognition of the limitations of anesthetized animals in the analysis of cardiovascular regulation. Van Citters, Franklin, and Rushmer (4, 12) emphasized the loss of sinus arrhythmia and stabilization of heart rate caused by anesthesia. Others have described an initial decrease in total peripheral resistance following induction with barbiturates (7). After the initial decrease, both total peripheral and femoral arterial resistance increased and remained elevated (1, 7). In contrast, a maintained decrease in total peripheral resistance occurs during desynchronized natural sleep in the cat and results in systemic arterial hypotension (14). This reduction was exaggerated after sinoaortic deaf-

ferentation and most likely results from dilation of resistance vessels (14). Vasomotor regulation during sleep in the cat, particularly desynchronized sleep, probably does not consist of uniform vascular adjustments (15). Localized areas of vasoconstriction are present even though the net effect is vasodilation. Anesthesia and natural sleep are thus quite different situations.

In an effort to define the interaction of system components more thoroughly, investigators have turned to the intact, unanesthetized, chronically instrumented animal; in addition to the results cited above, abundant evidence illustrates the advantages of studies in awake animals. An appropriate example of the significance of the unanesthetized animal can be drawn from analysis of the regulation of cardiac output, the combination of heart rate and stroke volume. Both heart rate and stroke volume are affected by the autonomic nervous system. By changing autonomic balance, the same cardiac output can be attained by a change in either stroke volume or heart rate, or by some combination of both variables. An acute, anesthetized preparation tends to be limited to changing cardiac output by changing stroke volume alone, rather than displaying the true interaction between the two variables. There are other important differences in cardiac function. For instance, Hawthorne (16) found the change in base-to-apex length during the isovolumic phase of ventricular contraction in awake, intact dogs was about one-fourth of the change in open-chest dogs.

The contrasts between anesthetized and unanesthetized preparations have been sharpened further in several recent reports. Shubrooks (17) found higher gains for the carotid sinus response in the intact, unanesthetized dog compared to isolated sinus preparations. Adams, et al (18, 19) found no evidence of dominance of sympathetically - induced muscle vasodilation in the cardiovascular changes during fighting in the cat. They concluded that preparation for fighting usually produced changes opposite to those seen during fighting. The responses of fighting and exercise are similar, and the manifestations of an initial emotional state are superseded and masked by subsequent motor activity.

Also contrary to the findings in anesthetized animals, Bergamaschi, et al (20) found practically no effect on the resting coronary circulation or systemic hemodynamics following induction of beta-blockade in conscious dogs, a result supporting the report of Pitt, et al (21). A decrease in coronary blood flow following beta-blockade with propranolol can be demonstrated after stress such as excitement, exercise, and hypoxia (22). While such results indicate the caution required in extrapolation, reduced cardiac metabolism and coronary flow under stress would most likely be beneficial in humans with coronary arterial disease. Such a possibility would be excluded if reliance were placed solely on the results of acute studies.

The value of the chronically instrumented, unanesthetized animal is not restricted to the cardiovascular system. Mellor and Slater (23) studied daily changes in amniotic and allantoic fluid in pregnant ewes. One of their conclusions was, "The results from this study demonstrate clearly the value of using chronically catheterized animals, and it is suggested that their use in physiological studies on the conceptus must eventually supersede that of acute, anesthetized preparations." Many other similar examples could be given.

The joining of an increased appreciation of the above factors with technological advances has led to an accelerated use of the chronic preparation. Futhermore, the detailed properties of complex, non-linear regulatory systems require complex, multi-variable analyses. By combining instrumentation progress with expanded data-processing capability, many more variables can be analyzed simultaneously. Progress in this area will provide an additional bridge to understanding the relationships between animal and human physiological processes, and ultimately contribute significantly to the advancement of human welfare.

KEY WORDS

Because of the significance of the chronically instrumented animal, especially in cardiovascular research, and the need to summarize the current status of the techniques used in these studies, a Symposium was held to discuss this subject. The contents of this book were derived from the presentations at the Symposium. That this meeting was possible indicates the advances in our ability to obtain this type of cardiovascular data, as well as the new horizons for the understanding of dynamic system properties which are opened by this experimental design.

We are asked regularly for a selection of key words to identify the essential elements of a scientific communication. The question of the value of key words as an aid in solving knowledge explosion problems is unresolved, but the idea appears worth the effort. Certainly the essence of this book is contained in the title; the major concern is with implantation of devices for measurement of cardiovascular variables for prolonged periods.

Therefore a meaningful selection of key words could well be "dynamic", "intact", and "chronic", as opposed to "static", "isolated", and "acute". This contrast embraces the real significance of the contents of this book. Typical applications of these techniques include studies of dynamic stress states such as exercise and changes in acceleration levels. There are promising possibilities for relating cardiovascular and behavioral changes, and for more meaningful analysis of the effects of pathological processes

such as heart block and anemia.

OBJECTIVES

The growth of knowledge and capability in this area made it mandatory to consolidate a great deal of knowledge scattered through the literature, or carried in the minds of individuals and not recorded at all. This lack of coordination has created great problems for the new user, or for the researcher attempting to evaluate the literature. The need for collecting this information was clear and the meeting provided a focal point for this major objective.

There were other important objectives. The need for establishing a benchmark for measurement of future progress was also great. The material in this book provides a base against which new developments can be compared, permitting better judgment of usefulness of a new approach and increasing the likelihood of true progress. The areas of deficiency are also evident, and indicate where effort is needed to make the most significant advances.

Other points important to easier and more widespread use of these techniques are discussed in the text. Differences in the characteristics of species need to be considered as part of the experimental design. What are the essentials of animal care which will best combine humane treatment with experimental success? What are the relative merits and deficiencies of the many types of available transducers? When is telemetry more economical in the long run? What types of information can be most satisfactorily handled by analog techniques? What are the advantages and disadvantages of digital processing? These are difficult and challenging questions. There are many ideas and experiences in these areas, and findings need to be compared to reach a consensus, or to indicate areas of deficiency needing more information before the question can be answered. This volume is intended as a beginning in answering these questions.

DEFINING THE CHRONIC PREPARATION

Interpreting the meaning of the word "chronic" is an especially difficult task. Various researchers have construed "chronic" to mean many things. The word has been used to describe experiments on animals one to two days following surgery, prior to the return of what could be called acceptable physiological function. This is not the meaning used in this book. A more appropriate synonym for *chronic* is *prolonged*. The two major factors important to the interpretation are (1) satisfactory return of

the animal to its control state, including absence of any signs of infection, and (2) proper function of the implanted device. Ample evidence has been assembled over the past years that many of the commonly used anesthetic agents are still present in the blood stream of the animal as long as 72 hours after use. This means the animal has not fully recovered from the operative procedure prior to this time, and thus could not be termed a chronic animal. Local anesthetic agents are an exception, since their use is generally restricted to procedures for implantation of catheters or other similar devices readily introduced without the need for general anesthesia.

The type of implantation procedure must also be considered in determining the time required for complete recovery. Chest surgery is likely to require the longest time for return of acceptable function, with other types of surgical approaches requiring minimal amounts of time.

Judgment of the investigator and his colleagues is required to reach agreement regarding the degree to which the preparation may be considered "normal." Many "chronic" animals have been prepared which were a success from the surgical standpoint, but a total failure because of the condition of the animal. This type of work can be avoided and should not be termed chronic.

The general health of the experimental subject is also a crucial factor. The general health and surgical tolerance of the animal are intimately related and must be considered together. For example, most bacterial infections affect the cardiovascular system directly or indirectly. Certain infectious processes may require prolonged periods of time to develop, and the possibility of infection requires continued attention. Body temperature, hematocrit, hemoglobin, and leucocyte count should be checked before and after instrumentation of the animal. These values should be within an acceptable range for the particular animal subject before the term "chronic" is applied.

The function of the implanted devices will depend on their nature or principle of operation. Catheters are usable as soon as they are implanted, as are solid state pressure transducers. Usually, flow probes will not function immediately, depending upon the relationship between the probe and vessel wall. In most cases, time must be allowed for fibrous tissue formation around these devices. This insures proper electrical contact as well as protection against vascular rupture. This overgrowth process generally takes 6-10 days in most animals. Similar amounts of time may be required before stable recordings can be attained from other electrical devices that depend on tissue contact.

To summarize the discussion at this point, a chronically instrumented animal is one in which all anesthesia from the operative procedure has left

the blood stream, acceptable physiological function has returned after implantation, and the implanted instrumentation functions adequately.

BOOK SECTIONS

The succeeding three sections of this book explore the practical implications of the points discussed above, with the papers from the Symposium organized into the topics of Transducer Characteristics, Implantation Techniques, and Signal Conditioning and Processing. Before describing the relevance of these topics, the careful thought necessary in making the decision to use a chronic animal should be reemphasized.

From the above definition of a chronically instrumented animal, it is quite obvious that this path of physiological research is not an easy one to follow. Good chronic preparations require much more time and money than acute experiments. In most institutions, the cost of conditioned animals is greater than for common pool animals. This selected animal usually must be held for an additional period of time before surgery, thus adding a maintenance cost, and hopefully will be kept for months after surgery at an additional maintenance cost. The various implanted devices are expensive, and a single animal preparation such as the dog may easily cost $500 or more, depending upon the price of the instrumentation. Therefore the first requirement imposed on the investigator is reasonable certainty that good design for the experiment requires a chronic preparation.

Once this decision is reached, the next logical step is selection of the variables to be measured. The basic variables in cardiovascular research are pressure, flow, and dimension. Whether one is referring to the intact circulation or a system of tubes, these three quantities are essential to the description of the function of any segment. From these measurements, most other quantities currently used in cardiovascular research can be derived. At present, the three basic variables can be measured fairly well with existing instrumentation available from commercial sources. In the past, design of the chronic experiment was frequently limited because of lack of a transducer. Now the reverse is becoming true: the large numbers of available transducers create a new problem in selecting the one most appropriate to the experimental design. Furthermore, as the number and types of instruments increase, the need for communication increases. Therefore Section II reviews factors affecting choice of instrumentation and describes the characteristics of those types in common use.

After selection of the variables and the transducers, the next steps are choosing the most appropriate animal, implanting the measurement devices, and attaining a true chronic preparation. The concerns affecting these steps

are defined in Section III.

The final phase of this sequence is data processing. Since all the other steps are simply preparatory to this one, suitable data handling techniques are crucial to a successful result. This is particularly true in the case of the chronic experiment since streams of continuous output are usually generated. Some basic examples, as well as more advanced and comprehensive procedures, are discussed in Section IV. This is also the area of greatest developmental need and is likely to be emphasized in future presentations.

The papers were provided by active researchers whose previous publications clearly marked them as major contributors to the subject. The papers were reviewed and revised as necessary. After each major section was presented, lengthy discussion sessions were held. The discussants were a mix of both active users and those considering use but not yet experienced. The discussions were condensed and edited to include additional points not part of the original papers, and to emphasize especially significant points. The summarized discussions appear at the end of each section.

The papers and discussions stress practical concerns rather than the theoretical, and should be readily understood by anyone active in the field as well as those with only a peripheral acquaintance with the subject. In addition, the book will be particularly valuable to those who wish to use these techniques but have not yet done so, and will be of interest to those not active in the field but concerned with understanding the research results obtained using this methodology. Anyone engaged in instrumentation development will also find it useful.

SUMMARY

This book should increase the availability of experience leading to optimum performance from existing techniques, improve the communication of new techniques, and expand communication between instrument designers and users. The ultimate goal is to advance the understanding of system properties and regulatory processes through more widespread use of the chronically instrumented, intact animal model.

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II. TRANSDUCER CHARACTERISTICS

Section Editor: Francis L. Abel

A. Selection of Instrumentation
B. Pressure
C. Flow, Electromagnetic
D. Flow, Ultrasonic
E. Flow, Indicator Dilution
F. Dimension
G. Acceleration
H. Electrodes
I. Discussion

2. CRITERIA FOR INSTRUMENT SELECTION

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It seems belaboring the point to emphasize that selection of a technique is absolutely essential to obtaining useful physiologic information, but many investigators seem to face remarkable difficulties in making such choices. In our laboratories we have long emphasized that experimental design grows naturally from a choice of a particular problem, and that selection (or even creation) of a technique follows naturally from the design. This is in sharp contrast to the general tendency of most investigators to use the techniques available in their laboratories, and to design experiments around available instruments rather than pertinent and important scientific questions; still, it takes almost as much time and energy to solve a trivial problem as an important one, and additional time spent on instrument selection, modification, or even design will appreciably expand an investigator's horizons. We urge others to consider this approach as well.

An investigator will tend to view instrument selection in one of several ways: (1) if he "knows" a technique, has used it successfully, and trusts himself to recognize when his answers are correct, he will be most comfortable with it; (2) he may select an instrument out of thin air, seeing its inner workings as some sort of "black magic" (or black box) whose proper functioning is a matter of faith or reliance on a manufacturer's representative; (3) he may rely heavily on an authority for assistance in the selection of an instrument; or (4) he may intelligently, even scientifically, choose the most appropriate measurement tool for his purposes on the basis of reasonable criteria. If he takes the last course, he must choose some criteria on which to make that decision.

Criteria on which instrument selection is based grow, as mentioned earlier, out of the needs of the experimenter for a certain kind of data needed to answer a specific problem. For this reason there cannot be a "best" way of measuring pressure, or dimensions, or flow, or any other

cardiovascular variable until the experimental design has been established. There are some general rules we can use, though, in constructing such criteria, and we suggested some ("at the risk of inciting controversy" which never really appeared) for evaluating flowmetering techniques which could be applied to other physiologic variables as well (1).

1. *Accuracy:* We defined accuracy as the overall conformity of a measurement obtained in a certain way to the actual value of the target variable sought. Despite the natural desire of an investigator to obtain 100% accurate measurements of his target variable, this is impossible in practice; in general, we rarely see experimental requirements for accuracy which exceed tolerable errors of ± 10%, which appears to be the limit for many techniques anyway. One way of modifying experimental design to meet the limitations of a technique's accuracy is to compare changes with some reference, or control, measurement, for often scaling errors remain unchanged with changes in physiologic state and information obtained in this way can meet the demands of the investigator.

Accuracy includes several other technique variables which must often be addressed:

a) Directness: how closely does the measured variable correspond to the target variable? Measuring flow by detecting pressure gradients is somewhat indirect, while volume plethysmographs used to determine changes in limb size are quite direct.

b) Uniqueness: how much is the measured variable influenced by variables other than the target variable? Pressure measured with a catheter-manometer system may be influenced by gravitational forces, a hydrostatic head; pressure measured with a catheter-tip manometer may be influenced by temperature changes if the sensor is temperature-sensitive.

c) Stability: how much does the measured variable tend to change (as a function of time) with respect to the target variable - i.e., how much does it drift? Implanted manometers tend to change their output due to stress-relaxation or creep in the construction materials, for example. The rate at which an instrument drifts can be crucial, and its satisfactory use dependent in turn on how often one can recalibrate the device, and whether it can be recalibrated *in vivo*.

d) Reproducibility: Assuming the target variable has not changed, how much does the measured variable change? We sometimes refer to this as "test-retest correspondence." Some techniques tend to underestimate or overestimate by a fixed amount, and have high reproducibility in the face of limited absolute accuracy. Investigators studying changes in cardiovascular variables as a function of time, as in the study of progressive induction of disease, often face high demands for reproducibility. Korotkoff determin-

ations of blood pressure in the same individual may have a high or low degree of reproducibility, depending on the investigator.

e) Nonreactance: how much does the act of measurement influence the measurement obtained? Measuring cardiac output by cutting the aorta and allowing an animal to bleed into a bucket obviously influences the measurement obtained; on the other hand, measuring flow velocity in a superficial artery with a transcutaneous Doppler flowmeter probably influences the target variable very little. In general, the more direct the measurement obtained the more intervention one must tolerate and the higher the biologic reactance; this is one example of the sort of "design tradeoff" which must be faced in deciding on a technique.

f) Sensitivity: how well does the technique detect small changes in the value of the target variable? The usual limitation on sensitivity is the "noise" - electrical, mechanical, even physiologic - in the system under examination; when the signal-to-noise ratio approaches unity the ultimate sensitivity of the system has been found. Occasionally one may employ data processing techniques which reduce noise, or increase the signal level, in order to improve sensitivity.

g) Range: what is the difference between the largest and smallest recordable variable? Most instruments have both an upper and a lower limit of usefulness, which can sometimes be extended for certain applications. A manometer has an upper limit dictated by its construction, which will fail when the device is overpressurized. Some transducers have a certain linearity (defined as the constancy of the ratio of target variable to measured variable over the range of interest) over limited ranges, with linearity gradually being compromised as these limits are approached.

h) Sampling rate: how well will the technique follow rapid changes in the target variable? Other phrases for this characteristic are fidelity and frequency reponse. A general information theorem states that the upper limit for sinusoidal frequency response will be one half of the sampling rate, or the rate at which a new measurement is obtained. An electromagnetic flowmeter which samples flow every hundredth of a second, for example, cannot show harmonic components in the flow waveform which exceed 50 Hz. Incidentally, in practice we usually find that the output of the instrument system is usually compromised further by adding a filter somewhere; most thermal or ink-writing oscillographs cannot drive pens much faster than about 100 Hz and thus biologic information at frequencies higher than this is lost, and most electromagnetic flowmeters are limited to about 25-30 Hz by filters installed in the instrument.

2. *Utility:* No matter how good an instrument or technique might be, it is useful only insofar as it may be employed in a practical situation. Con-

sideration of utility must include both the source of data (some techniques useful in chronically instrumented animals cannot be used in man, for example) and the laboratory setting (an open plain in Kenya is not equivalent to a well-equipped laboratory in San Diego), and often accuracy must be compromised within acceptable limits in certain studies because the most accurate techniques cannot be used.

a) Applicability: in how many different sites can the technique be used? Electromagnetic flowmeters work well on larger vessels, but cannot be employed in arterioles; Korotkoff determination of blood pressures is suited for application in the extremities but not in the central arteries.

b) Selectivity: how specific is the technique for measuring at the site needed? Measuring muscle blood flow via a plethysmograph necessarily includes measuring skin blood flow as well; on the other hand, an electromagnetic flowmeter is highly selective for blood flowing through the vessel around which its transducer is placed.

c) Flexibility: while it is not a crucial consideration for a specific experimental need, how flexible is a certain technique? Can it be applied to other questions likely to arise in the future, or is it limited to a specific application and no other? Are there a variety of experimental conditions in which it may be employed, or can it be used only under very restricted circumstances?

d) Versatility: how easily can the technique be modified to suit other experimental needs? Ultrasonic transit-time techniques can be used to measure flow or dimensions, for example, as detectors in gas chromatography, or in other applications. Electromagnetic flowmeters measure flow of conductive materials, period.

e) Convenience: how long and how hard is it to get the technique ready for each experiment? One of the reasons that pulsed ultrasonic flowmeters never became popular was their complexity; a highly skilled technician with a battery of testing instruments, making adjustments over several hours, was required to set up a group of three or four flowmeters with a synchronizer. Electromagnetic flowmeters are much more easily set up. Doppler ultrasonic flowmeters do not require precalibration. Most of all, one must decide whether he can use a technique intelligently - if not, it is bound to prove inconvenient.

f) Portability: does the technique lend itself to making measurements under circumstances in which moving large, bulky equipment is impractical or impossible? Is it portable in the sense of being carried by an instrumented animal (or man) with telemetry or local recording? Can it even be moved from one lab to another without a major effort, as is usually true with X-ray techniques? In many experimental studies portability is of no

consequence, but in others it may be an extremely important consideration.

g) Crosstalk: does the technique interfere with other measurements being made simultaneously, using other devices? We often face a severe interference problem in attempting to use sonomicrometers at the same time as electromagnetic or Doppler flowmeters, for example.

h) Cost: how much will it cost, both in time and money, to acquire the instruments and become familiar with them? How much will it cost to analyze the data in the form this technique yields? What are the associated costs with using and maintaining the equipment, both in parts and personnel? This is obviously important to all of us, and the major problem in assessing costs appears to be unfamiliarity with hidden costs - especially the time required.

i) Availability: is the instrument commercially available or will the experimenter have to construct a device himself? How about service? In our experience, constructing almost any instrument will cost several times the price of a commercially available device with the same specifications. Improving a commercial device to meet special specifications is less expensive than constructing one from scratch, too. The major reason for this situation is that it takes a long time to construct something, make it work, debug it, and confirm that it meets specifications. It takes an inexperienced constructor longer to make something than a manufacturer who has made dozens, and though the parts cost for an item may be less than the finished product, the investment in time can be enormous. Moreover, often there are subtleties of operation which require months to work out in constructing something yourself, and the cost of throwing away inaccurate data (as we once had to do because of a flaw in a Doppler flowmetering system which escaped us for several months) is incalculable.

SUMMARY

We can summarize the problem faced by an investigator in choosing a technique or an instrument by emphasizing that there are no easy or universal choices, no matter what his variable of interest or experimental circumstance. First, he must define his problem in terms which can be satisfied by the measurement of a physical variable; then he must define the circumstances under which the measurement must be made to meet the demands of the experimental design; and only then can he choose which of the several techniques available are best for him.

A variety of other considerations must also be included in any criteria he may choose, and because these must be *his* criteria he must establish a set of his own priorities quite early. We have found that exposure to principles of instrumentation, and training in understanding instruments is

especially useful to the investigator who does not want to be limited to those techniques already in his laboratory, and urge those of you without such training to seek it.

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3. EVALUATION OF MINIATURE PRESSURE TRANSDUCERS[1]

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Pressure measurement is an integral component of many chronically instrumented animal preparations. Indirect techniques cannot be applied to essential but inaccessible parts of the vascular tree. All indirect methods contain significant uncertainty and inaccuracy, and continuous sampling of absolute values is extremely difficult. Direct approaches can be applied to all major vascular segments, have the highest accuracy available, and provide continuous values with as much waveform detail as desired. For these reasons, direct techniques are the method of choice for the chronic preparation.

There are two basic methods of direct pressure measurement. A catheter may be used to connect the transducer to the measurement site, or the sensing element may be implanted inside the vascular system. The use of a catheter can cause errors from interaction between the pressure wave and the catheter characteristics such as wall compliance and the presence of trapped air bubbles. The intravascular sensor avoids these problems, but new ones are created which are not as fully understood as those of catheters.

The relatively new transducers using solid-state elements permit the miniaturization required for intravascular measurements, as well as recording fidelity much improved over that available with a catheter system (1). The association of increasing demand with rapidly advancing technology has led to a wide range of small transducers with a spectrum of characteristics from which to choose (Table 1). The wide range of choice is certainly a desirable situation, but now the investigator is faced with the problem of selecting the transducer which is most appropriate for the required measurement, with continuing need for adequate testing and evaluation of the measurement system.

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The purpose of this paper is to provide data on the characteristics of a number of commercially-available units as an aid to the investigator in choosing the transducer most appropriate to the experimental requirements. In addition, testing procedures are described which will produce a higher level of continuing success in the use of these instruments.

GAUGE SPECIFICATIONS

The first step in evaluation is standardization of the manufacturer's specifications (Table 1). The essential characteristics include size of the sensing element; excitation voltage, indicating the nominal voltage required for driving the sensing element; volumetric compliance, indicating membrane displacement for a given pressure increment; pressure range expected for normal use; over-pressure, indicating the maximum force which the gauge can withstand without destruction; and sensitivity, indicating voltage output for a given pressure level. Static error includes hysteresis and non-linearity, temperature sensitivity, and stability. Hysteresis and non-linearity summarize static accuracy and reproducibility of output for the measurement range; and temperature zero shift indicates the error caused by effects of temperature on sensing element balance. The remaining major characteristic is dynamic response, indicating the range of frequencies for which accurate reproduction can be expected. The units of expression are quite variable between manufacturers, but they should all be able to provide basic information on the above characteristics. Standardization to the same units permitted initial comparisons between transducers. Examples of the types of gauges available are shown in Figure 1.

TABLE 1

SPECIFICATION RANGE FOR INTRAVASCULAR TRANSDUCERS

DIAMETER	EXCITATION	VOLUMETRIC COMPLIANCE	PRESSURE RANGE	OVER-PRESSURE
mm	DC Volts	$\frac{ml}{300\ mmHg}$	mmHg	mmHg
1.7 to 7.0	3.8 to 10.0	.09 to 1×10^{-6}	-300 to 300	500 to 1500

GAUGE SENSITIVITY	STATIC ERROR			DYNAMIC RESPONSE
	HYSTERESIS AND NON-LINEARITY	TEMPERATURE SENSITIVITY	STABILITY	
$\frac{mv}{300\ mmHg}$	% Full Scale at 37°C	mmHg / °C	mmHg/hr	Hz
1.5 to 100	± 0.4 to ± 1.0	± 0.1 to ± 2.0	0 to 8	DC to 200,000

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Fig. 1. Nine intravascular pressure gauge tips, indicating the relative sizes of sensing areas. Top to bottom (left): Biotec BT-250T, Whittaker 1017, Micron MP-10, Konigsberg P-21, Sensotec SA-SA M7BWE; (right): Konigsberg P-19, Honeywell MCP-070-7F, Whittaker 1007, Millar PC-300. Reproduced, by permission, from *Anesthesia and Analgesia* 51:746, 1972.

STATIC TEST METHODS

The diameters were checked with calipers and were accurate. The manufacturers' specifications for volumetric compliance, pressure range, and over-pressure were accepted as stated.

Excitation. The gauges may be connected to any standard DC or AC pressure amplifiers; we use either a Honeywell 1508 Visicorder or Beckman type RM Dynograph recorder. The standard amplifier excitation voltage may be used or it may be adjusted to a lower level, since lower excitation voltages may improve temperature-dependent stability. No other special voltage regulation is necessary.

Sensitivity. No special measurements of sensitivity are necessary. The output of all gauges is adequate for use with standard pressure amplifiers. However, the gauges with relatively high output are less sensitive to thermal effects since such changes represent a smaller percentage of total output.

Accuracy. Hysteresis and non-linearity can be evaluated by subjecting each gauge to 25 mmHg pressure increments from 0 to 300 mmHg, followed by 25 mmHg decrements to zero pressure. The sequence should be repeated a minimum of 3 times for each gauge.

Temperature Sensitivity and Stability. The amplifiers and gauges should be allowed to warm up briefly. The special temperature-sensitivity of the miniature gauges requires both short-term and long-term testing in a Haake temperature-controlled water bath. For evaluation of short-term stability, output is monitored while the water-bath temperature is repeatedly cycled over the range of 37± 5°C. Long-term stability is tested by monitoring output while maintaining water-bath temperature at 37°C for a minimum of three hours. Normal body temperature is appropriate because it is closest to the circumstances of use and because large zero shifts consistently occur during acute experiments when gauges are transferred from a 22°C (room temperature) to 37°C environment. Since the zero reference must be established in the water bath at 37°C, transfer to the vascular system requires a brief transition through air. This transfer creates a transient, but severe, thermal stress as a result of evaporation from the transducer face. To evaluate the stability of the gauge under these conditions, the gauge is removed from the water bath, held out for 60 seconds, then returned to the water and the resulting zero shift measured.

DYNAMIC TEST METHODS

We have compared a number of test approaches for estimating system response to dynamic pressure changes. These test inputs included balloon

pops, sharp taps or thumps, square waves from a special hydraulic generator and from an oscillator-speaker combination, and sinusoidal pressure waves from a mechanically-driven piston and from the oscillator-speaker. The pops, taps, and thumps were discarded because of inability to control consistently the magnitude and reproducibility of the input disturbance. The hydraulic square wave system was described by Levasseur, et al (2) and gives a satisfactory, reproducible input. The piston-type oscillator (3) is awkward, cumbersome, expensive, and the maximum frequency of 60 Hz supplied with our model is a serious limitation since a frequency response of 100 Hz is required if the signal is differentiated (4). The oscillator-speaker system produced sinusoidal signals flat from 1 to 100 Hz as well as square waves, and is by far the most satisfactory (Fig. 2). It is similar to those described by Stegall (5), Henry et al (6), and Vierhout and Vendrik (7), and is available from Millar Instrument Co., Houston, Texas. The system consists of a Wavetek model 130 function generator, a constant-current amplifier, and a University loudspeaker with an attached test chamber composed of a Lucite cylinder. The transducers or tips of catheters to be tested are inserted into the cylinder chamber. The cylinder was modified for multiple ports in the wall permitting simultaneous testing of several gauges. For the dynamic tests, the transducer outputs are recorded on a Hewlett-Packard 1201-B storage oscilloscope.

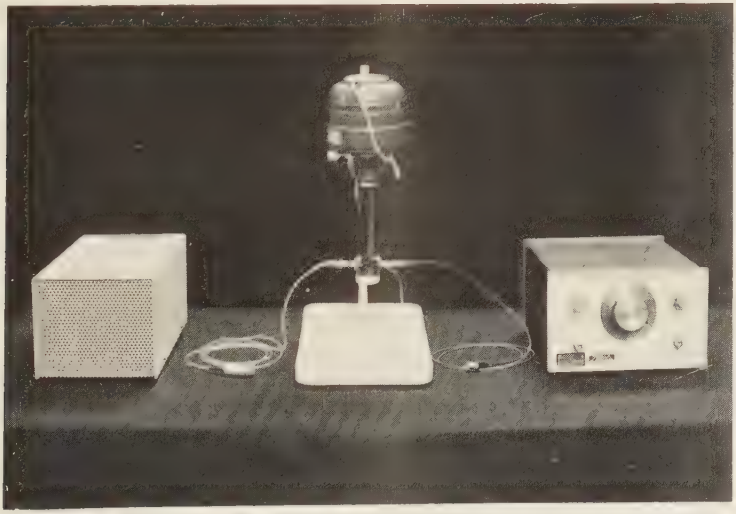

Fig. 2. System used to test miniature gauges (Millar Instrument Co.). Gauges are inserted at the lower end of the Lucite chamber. The system can be operated in both sinusoidal and square wave modes. Reproduced, by permission, from *Anesthesia and Analgesia* 51:746, 1972.

A suitable variable for tests using a sinusoidal input is the response amplitude at each frequency. A reference determined from the average value of the amplitudes with less than one per cent variation allows for small deviations in the oscillator characteristics; the response may be assumed flat until the amplitude exceeds five per cent of the reference. As a general rule, this oscillator will not reach the resonant frequency of a miniature pressure cell when operating in the sinusoidal reference mode. However, the resonant frequency can be estimated by using a square wave input to the pressure generator. For square wave inputs, the frequency of the major oscillation following the downward leg of the step change in pressure is the resonant frequency. An example of the response of a catheter-manometer combination is shown in Figure 3a. The much higher resonant frequency of a catheter tip gauge is shown in Figure 3b.

A simple alternative for obtaining resonant frequency has been suggested by Konigsberg (personal communication). The transducer may be located in air or, preferably, in a water tank. A pressure transient can be produced by a hand-clap (for a sufficiently sensitive gauge) or by firing a blank pistol positioned about two feet from the transducer and aimed approximately one foot to its side (for a less sensitive gauge). Measurement of the response requires an oscilloscope with the sweep rate set fast enough to detect the transducer oscillation and avoid the much lower frequencies resulting from secondary oscillations produced in the room or water tank. These transducers are essentially undamped, even in water, so the flat response is assumed to be 10 per cent of the natural frequency.

The advantages of a primary standard could be realized by generating pressure oscillations in a tank with a piezoelectric crystal; the frequency would be determined by the crystal and its oscillator, and the exact amplitude of the pressure wave could be measured using Schlieren techniques.

TYPICAL CHARACTERISTICS

The static error specifications are usually within the limits of reading accuracy and should not exceed the specified values (Tables 2 and 3). Average temperature zero shifts are variable but generally acceptable if zero is established at 37°C. The return to zero after exposure to air is somewhat more variable and usually produces a shift which is additive to any shift produced by fluid temperature changes alone. In every operative gauge, the region of flat frequency response exceeds 100 Hz. Resonant frequencies are generally greater than 1 KHz. Konigsberg (personal communication) obtained resonant frequencies ranging from 33 to 166 KHz in air and 20 to 50

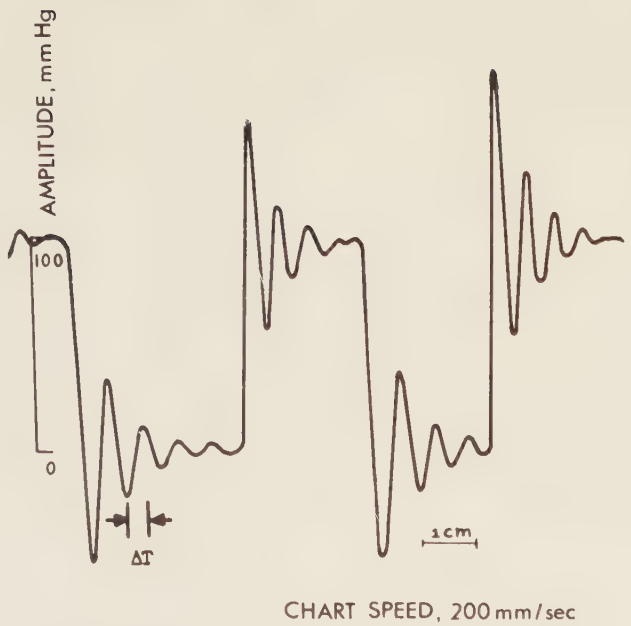

Fig. 3a. Response of Statham P23GB with a No. 6 Cournand catheter (100 cm long) to a square wave input. Reproduced, by permission, from *Anesthesia and Analgesia* 51:746, 1972.

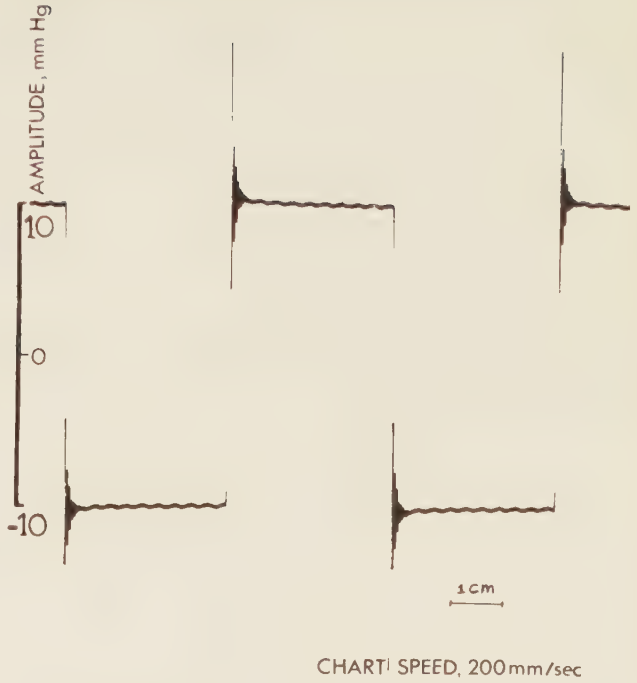

Fig. 3b. Response of a catheter tip gauge (Millar Instrument Co.) to a square wave input. (Note differences in pressure calibrations).

TABLE 2

INTRAVASCULAR PRESSURE TRANSDUCERS

MANUFACTURER & MODEL	DIAMETER mm	RATED VOLUMETRIC COMPLIANCE $\frac{(mm)^3}{300\ mmHg}$	NOMINAL PRESSURE RANGE mmHg	RATED OVER-PRESSURE mmHg	RATED[1] SENSITIVITY $\frac{mv}{300\ mmHg}$	STATIC ERROR RATED % F. S. at 37°C	STATIC ERROR TESTED % F. S. at 37°C
KONIGSBERG[2] P-21	7.0	20.1×10^{-3}	0 to 300	1000	10.5	± 0.4	within specs
BIO-TEC BT-250-T	6.5	Not Available (Very Low)	0 to 300	1000	30.0	± 0.8	within specs
WHITTAKER 1017	6.5	15×10^{-3}	-50 to 300	750	30.0	± 1.0	within specs
SENSOTEC[3] SA-SA M7BWE	6.4[4]	.09	-100 to 300	500	80.0	± 0.8	within specs
MICRON MP-10	6.2	Not Available (Very Low)	-50 to 300	1500	31.0	± 0.5	within specs
KONIGSBERG P-19	5.0	6.9×10^{-3}	0 to 300	1500	30.0	± 0.8	within specs
HONEYWELL MCP-070-7F	2.3	$< 1 \times 10$	0 to 300	1000	15.0	± 1.0	within specs
BIO-TEC BT-5F-3	1.7	Not Available (Very Low)	0 to 300	600	10.0	± 0.8	within specs
WHITTAKER 1007	1.7	$.9 \times 10^{-3}$	0 to 300	1500	1.5[5]	± 1.0	within specs
MILLAR P-C-300	1.7	6×10^{-3}	-300 to 300	1500	100.0	± 0.5	within specs

1. For 10 v. DC or RMS excitation, 0-300 mmHg range. At this level of excitation most gauge compensation networks contain voltage dividers to reduce bridge voltage; almost all work better at minimum (< 5v) excitation (depending on characteristics of temperature compensation network).
2. 4 gauges tested.
3. 2 gauges tested.
4. Transducer flat, oriented in same axis as lead wires.
5. Reduced from 20 mv in attempt to obtain temperature stability.

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TABLE 3

INTRAVASCULAR PRESSURE TRANSDUCERS

TEMPERATURE ZERO SHIFT AND SHORT TERM STABILITY[1]

	RATED	32 to 42° TESTED		WATER-AIR-WATER		3 HOURS at 37°	
MANUFACTURER AND MODEL NUMBER	MAX. CHANGE mmHg °C	MAX. CHANGE mmHg °C	AVG. CHANGE mmHg °C	MAX. CHANGE mmHg	AVG. CHANGE mmHg	MAX. CHANGE mmHg	EXCITATION DC Volts
KONIGSBERG[2] P-21	±0.2	0.2 to 2.5	0.2 to 2.0	0.3 to 0.5	0.1 to 0.3	0.5 to 2.3	5.0 to 9.0
BIO-TEC BT-250-T	±1.0	0.3	0.2	0.2	0.1	1.4	5.3
WHITTAKER 1017	±2.0	0.7	0.6	1.0	0.3	0.5	10.0
SENSOTEC[3] SA-SA M7BWE	±0.2	0.4	0.2	0	0	2.5	5.0
MICRON MP-10	±0.9	0.3	0.3	0.5	0.2	2.2	4.6
KONIGSBERG P-19	±0.6	0.7	0.6	0.5	0.2	1.0	5.0
HONEYWELL MCP-070-7F	±0.1	1.0	0.8	3.0	2.0	24.0	5.0
BIO-TEC BT-5F-3	±1.0	1.0	0.8	0.3	0.1	2.0	5.5
WHITTAKER[4] 1007	±2.0	102.0	76.0	30.0	30.0	0	3.8
WHITTAKER 1007	±2.0	1.2	0.6	0.3	0.3	4.0	10.0
MILLAR P-C-300	±0.2	0.3	0.2	0	0	0	5.6

1. Primarily determined by adequacy of temperature compensation and flow sensitivity; water at 37°C.
2. 4 gauges tested.
3. 2 gauges tested.
4. 8 gauges tested. Two representative examples selected.

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KHz in water. The changes noted with one of the Whittaker 1007 samples illustrate the results from a defective and unusable gauge.

APPLICATION CONSIDERATIONS

Placement of the transducer inside the vessel eliminates the errors caused by catheter properties, and the numerous available models testify to the popularity of this approach. The intravascular gauges avoid the problems of a fluid column, but introduce several new difficulties. Clotting is always possible, and fibrin deposits on the transducer surface could change its frequency response or other characteristics. For most users this has not been a serious limitation, and various anticoagulant procedures are available. Sensitivity to lateral pressure is of real concern in certain applications. For instance, special considerations apply in an acute, open-chest animal with a heart almost emptying with each beat. Under these conditions, the contracting myocardium can produce side-loading of the transducer case which can severely distort the baseline and make accurate pressure determination impossible. The Konigsberg P-21 case has been specially strengthened to reduce this effect, and it is manageable. However, we have found a flat design, such as the Sensotec or the Konigsberg P-16, to be best for these uses. This problem is minimized when the gauge is chronically implanted, since a closed-chest animal has a larger heart and smaller ejection fraction.

By far the greatest potential difficulty with these intravascular gauges is susceptibility to flow-induced changes in heat dissipation. Changes in temperature can change sensing element resistance, and the major determinants of heat transfer to the medium are flow velocity, temperature of the diaphragm, and evenness of distribution of the heat. Any thermal-dependent resistance variation may appear as zero baseline drift or even waveform distortion. All of these transducers behave well in air, which is often the way they are tested by the manufacturer, because air is a relatively good insulator compared to water. We therefore test them in a temperature-controlled water bath. The usual type of bath operates with circulating or stirred water, and some transducer designs will be sensitive to this flow even though the water temperature is constant. Although a larger diaphragm surface provides a more adequate heat-sink, special care must be taken in manufacturing to avoid hot-spots. In acute applications, the zero reference can be established at 37°C to avoid the large shifts frequently produced when the gauge is transferred from a room temperature environment into the vascular system. In chronic implants, precise calibration requires comparison with an acutely-placed system.

Operation at the lowest possible excitation voltage may result in improved stability, since sensing element current will be reduced and resistive heating will be decreased. The smallest diameter or catheter-tip gauges are particularly susceptible to temperature effects since the small tip area reduces the effective heat sink, and maintaining consistent production quality is much more difficult.

Both static accuracy and frequency response of the intravascular gauges are invariably excellent, far exceeding the minimal requirements for pressure measurements. The very stiff diaphragms and intravascular placement are optimal combinations when maximum waveform fidelity is required.

Our experience indicates the tests outlined in Tables 2 and 3 are essential to establish the characteristics of any individual gauge, regardless of the specifications or test procedures described by the manufacturer. On occasion, new gauge configurations adapted from wind-tunnel designs have been introduced without proper modification for biological uses. An excessively high frequency response increases the likelihood of irreversible damage from pressure transients, such as those created when the gauge is inserted into the vascular system. Furthermore, a gauge stable in air may be unstable in the higher thermal conductivity of water, and some manufacturers do not test their gauges in water. On occasion, gauges are damaged in shipping or with repeated use, and detection of the fault depends on appropriate testing. Gauge properties may also change during storage due to slight alterations in stresses between the bonded elements. Occasionally a change in properties of the glue bonding the semiconductor element to the diaphragm may occur as a result of humidity variations in the manufacturing facility (Konigsberg, personal communication). Some gauges with weak bonds have been detected by failure during testing. The frequency response measurement is especially useful for revealing this defect even though the full frequency range of the gauge cannot be determined. Static and dynamic testing before use is the best way to deal with these problems, and the gauge can be returned for replacement if defective.

All of these intravascular gauges tend to be fragile and very expensive, and they must be handled and maintained with great care. Because of the problems of quality control, temperature sensitivity, and durability, the largest intravascular transducer which can be used is likely to be the most satisfactory.

Precise, in vivo calibration is frequently somewhat difficult. A chronically implanted atrial catheter can be used to check zero of an intraventricular gauge (8). Acutely-placed catheter-tip transducers are useful for checking intra-arterial locations; the Millar PC-350 has been by far the best in our hands. In most cases, the zero drift of an implanted gauge occurs at a

constant rate and the sensitivity does not change. If desired, the sensitivity can be checked in a whole-body pressure chamber (9).

SUMMARY

Our experience indicates that great care is required in selecting pressure transducing systems, and every facility making pressure measurements should have access to a minimum capability for performing acceptance tests and repeated checks of transducers. This capability is basically a manometer system for applying static pressures, a temperature controlled water-bath (for testing temperature stability), and some type of hydraulic oscillator. A test series using this capability quickly reveals gauges with poor bonds or other manufacturing deficiencies, or those damaged in use, and comparison to the manufacturer's data is a guide to reliable sources of supply. Most importantly, the suitability of the operational characteristics to the intended use is substantiated.

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4. SILICONE RUBBER ENCAPSULATED FLOW PROBES FOR CHRONIC IMPLANTATION ON THE ASCENDING AORTA

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The electromagnetic flowmeter has gained wide acceptance as a means of measuring blood flow in arteries, veins, and within the cardiac chambers themselves. Probes may be constructed (1) or are commercially available for implantation on vessels from 2 mm in diameter up to 18 mm in diameter such as the dog's ascending aorta. The implantation technique has been described and animals may be prepared with flow probes chronically implanted on the ascending aorta and other vessels. These valuable animals can be trained to lie quietly or to exercise on a treadmill. They may be studied every day for months. However, sooner or later a dog which was healthy yesterday is found dead. Often in dogs with probes on the ascending aorta, death is caused by rupture of the aorta.

In order for electromagnetic flow probes to function well, they must fit tightly enough on the vessel for the electrodes to make good electrical contact with the vessel wall. Therefore it has been suggested that the flow probe produce a 10-20% stenosis of the vessel. A slight stenosis produces no adverse effect on peripheral vessels or on vessels which branch directly off the ascending aorta such as the coronaries. The ascending aorta, however, presents a special problem. It dilates with each systole as it receives the stroke volume, and then collapses as blood moves peripherally during diastole. A flow probe on the ascending aorta which fits tightly enough to provide good electrical contact during diastole will compress the adventitial vessels during systole.

Schlicter in 1946 (2), using a post-mortem injection technique, showed that the wall of the dog's ascending aorta is nourished by two systems of blood vessels. The vasa vasorum consists of an extensive adventitial plexus and a less extensive medial one. The major adventitial plexus supplies all the adventitia and the external half of the media. This plexus is supplied by

vessels arising from the main-stem coronary arteries and from the brachiocephalic and left subclavian arteries as they originate from the arch of the aorta. The lesser medial plexus arises from vessels which arise directly from the lumen of the aorta, and nourishes the intima and the internal half of the media.

Fig. 1. Photomicrograph of the ascending aorta in longitudinal cross section near the site of rupture. The internal half of the media appears normal, whereas the external half of the media is infarcted. The area that ruptured was under the proximal edge of the probe. Reproduced, by permission, from the *Journal of Applied Physiology*, 31:782, 1971.

Our evidence indicates that a tightly fitting aortic flow probe can compress the adventitial vessels, producing infarction of the adventitia and outer half of the media, which may then lead to aortic rupture and death. This is shown in Figure 1 which is a photomicrograph of an H & E section of dog ascending aorta which ruptured 29 days after implantation of a conventional rigid epoxy probe. It should be noted that the adventitia and approximately the outer one-half of the media shows necrosis with inflammatory cells. There was no clinical evidence of infection and bacterial culture of the aortic wall tissue was negative, therefore we believe that the inflammatory cells represented infarction of the wall. The intimal half of the media appeared normal histologically but was not strong enough to withstand the aortic blood pressure as evidenced by the aortic rupture.

In 27 of 31 previous gross specimens in which the aorta had ruptured, the site of rupture occurred on the inferior curvature at a point where the edge of the probe compressed the aortic wall. In the remaining 4 cases the rupture occurred on the superior curvature midway between the edges of the probe. Figure 2 shows a schematic diagram of dog aorta with flow probe implanted. Because of the curvature of the aorta the greatest pressure on the adventitial plexus would occur at the three points marked with an x. Our gross specimens demonstrate that the site of rupture occurred at one of these three points. To

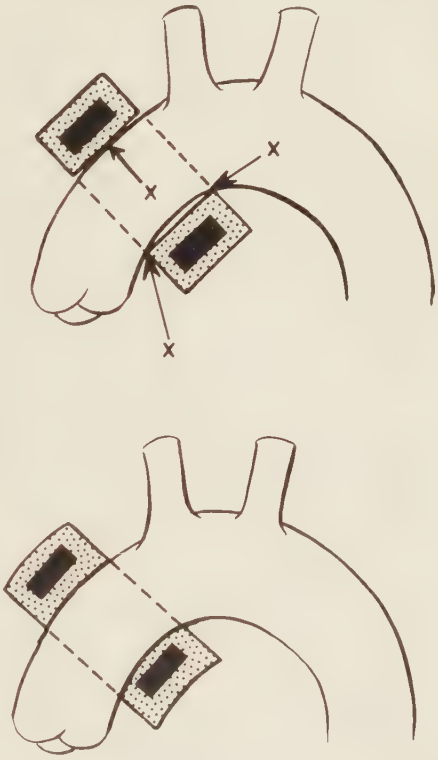

Fig. 2. Schematic diagram of a simulated flow probe implanted on the ascending aorta. Because of the curvature of the aorta, the greatest pressure on the adventitial plexus would occur at the points marked X. The bottom diagram shows how a flow probe may be constructed with a curved lumen to further reduce the pressure. Reproduced, by permission, from the *Journal of Applied Physiology*, 31:782, 1971.

reduce the pressure on these three points, two modifications in flow probe construction were made: First, the probes were given a final encapsulation in silicone rubber. This produced a probe which is slightly compressible and cushions the three surfaces at x. Secondly, the shape of the mold was altered to produce a probe which corresponded to the curve of the aorta as seen on the bottom. This should also reduce the pressure on the adventitial plexus.

FLOW PROBE CONSTRUCTION

Flow probes are constructed as previously described (1). It is necessary that the electrode lead wires be firmly fixed in epoxy so that they cannot move with respect to the magnetic field. Faraday's equation, e=Blv, describes the function of all electromagnetic flowmeters, both sine-wave and square-wave. B is the strength of the magnetic field and l is the distance between the electrodes which are in the flux of the field. The two parameters B and l must be kept constant so that the third term, v, which is the velocity of the blood, will be the only variable. Then the voltage e, measured at the electrodes, will be directly proportional to the blood velocity v. If the electrode wires are allowed to move in the field they will add a varying component of voltage which will make e a function of two variables instead of one. Therefore a completely rigid epoxy probe is constructed as shown in Figure 3a. The mold is constructed so that the two electrodes and the ground electrode extend into the lumen. Then the probe is placed in a second mold for a final encapsulation with silicone rubber. (Sylgard 187, Dow Corning Corp., Midland Michigan.) A coating approximately 2 mm thick is placed on the epoxy probe with the electrodes flush with the lumen as in Figure 3 b.

A comparison was made of survival times of five dogs with rigid epoxy flow probes and five dogs with silicone rubber encapsulated probes on the ascending aorta (3). The five dogs with rigid epoxy probes survived an average of 33 days and all five died from rupture of the ascending aorta. In the group with silicone encapsulated probes on the ascending aorta the average survival was 12 months, with three animals sacrificed for histological examination after 12, 13, and 14 months respectively.

Figure 4 shows a photomicrograph of an H & E section through the inferior curvature of the aortic wall in a dog which survived 14 months after implantation of a silicone rubber encapsulated flow probe. There is thinning of the media and some hyalinization of the medial and adventitial fibers. There are signs of pressure atrophy but no areas of necrosis. The pattern of damage follows that which would be expected from moderate pressure on the adventitial plexus, as described by Schlicter (2).

Fig. 3. A completed rigid epoxy probe is shown on the left, and on the right is a probe encapsulated in silicone rubber prior to removal from the Teflon mold.

TESTING ACCURACY OF SILICONE RUBBER FLOW PROBES

Although the electrodes are held in a fixed relationship with respect to the magnetic field, the internal diameter of the flow probe may change slightly. This would occur during systole when the silicone rubber layer is compressed slightly by the expanding aorta. It was felt that this slight

change in cross-sectional area may produce an error in the flow measurement. To test this, three dogs were prepared with both a rigid epoxy and a silicone rubber covered flow probe implanted side by side on the ascending aorta as previously described (3). In this way, flow could be measured simultaneously through a conventional rigid probe, and a silicone encapsulated probe. Flow was measured simultaneously with a Statham M 4000 gated sine-wave flowmeter and recorded at a paper speed of 50 mm/sec on a Sanborn 150 direct writing recorder. The cardiac output as measured by each probe was determined from planimetry of 10 cycles recorded simultaneously. This was done for the resting heart rate for each dog and at two elevated heart rates produced by isoproterenol infusion. The results are shown in Table I. The two measured flows varied from 3.4% to 6.6%. It was felt that this comparison was within the 5-10% accuracy one hopes to get from a device of this kind, and suggested that there was no significant

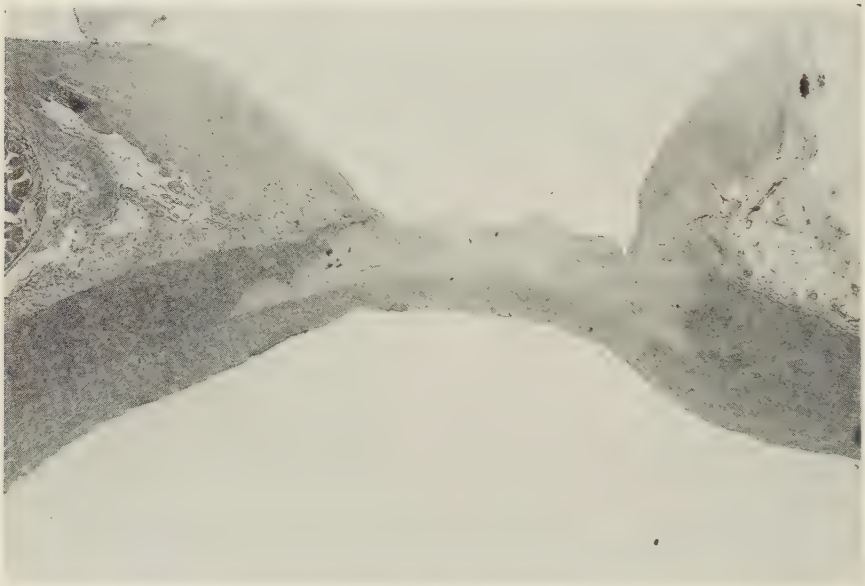

Fig. 4. Photomicrograph of a longitudinal cross section of dog ascending aorta which was intact 14 months after implantation of a silicone rubber encapsulated probe. The internal half of the media appears normal histologically, whereas the external half of the media and the adventitia shows pressure atrophy but no necrosis. Reproduced, by permission, from the *Journal of Applied Physiology*, 31:782, 1971.

difference in flow measurement between silicone encapsulated and rigid flow probes.

One other advantage of the silicone covered flow probe is that the electrodes make good contact with the vessel wall as soon as the probe is implanted. This allows the investigator to begin to measure cardiac output before the chest is closed.

The principle of silicone rubber encapsulation could also be used in the construction of ultrasonic flow probes. The silicone cushion would permit a tighter fit and better physical contact of the crystals with the vessel wall.

FLOW RECORDED IN THREE DOGS BY TWO FLOW PROBES PLACED SIDE BY SIDE ON THE ASCENDING AORTA

Dog Number	1	2	3
Heart Rate (beats/minute)	90	115	100
Rigid Probe Flow*	2.16	2.97	1.91
Silicone Probe Flow*	2.25	3.13	1.98
% Difference	4.17	5.2	3.70
Heart Rate (beats/minute)	125	135	140
Rigid Probe Flow	2.63	2.46	2.62
Silicone Probe Flow	2.72	2.59	2.79
% Difference	3.42	5.02	6.6
Heart Rate (beats/minute)	140	158	165
Rigid Probe Flow	2.93	3.27	3.18
Silicone Probe Flow	3.03	3.41	3.31
% Difference	3.41	4.28	4.09

*Probe Flow Recorded in L/minute

SUMMARY

Dogs with rigid electromagnetic flow probes chronically implanted on the ascending aorta often expire with a ruptured aorta. It was felt that the rigid probe compresses the vasa vasorum in the wall of the aorta and leads to infarction and subsequent rupture. Electromagnetic flow probes designed for chronic implant on the ascending aorta can be prepared with a final coating of silicone rubber. This coating permits the aorta to expand slightly with each systole, thus reducing the compression of the vasa vasorum.

Five dogs were prepared with rigid flow probes implanted on the ascending aorta. All five expired within 52 days from a ruptured aorta. Five more dogs were prepared with compressible silicone encapsulated flow probes on the ascending aorta and all five survived for a period of one year. An added advantage of the silicone covered flow probe is that the electrode will make good contact with the vessel wall as soon as the probe is implanted. This allows the investigator to begin to monitor cardiac output while closing the chest.

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5. A LOW POWER BATTERY–OPERATED ELECTROMAGNETIC FLOWMETER SUITABLE FOR IMPLANTATION

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INTRODUCTION

Totally implanted telemetry systems to measure temperature, ECG, and pressure are available, but telemetry of flow and flow velocity has been much more difficult. A major difficulty in obtaining a totally implanted system for flow detection has been the need to incorporate a self-contained power source. In order for such systems to have a reasonable operating life of at least a few months, the power consumption must be extremely low. Two flow measurement techniques currently have been demonstrated to be useful for such purposes in chronic animal preparations. Such systems have used ultrasonic and electromagnetic flow transducers and both normally take many watts of power. To develop a totally implanted system requires the development of low power circuits and a suitable implantable power source.

Multichannel implantable telemetry systems which provide pressure and ECG data have demonstrated the value of totally implanted systems for chronic animal studies (1). The measurement of other parameters such as flow is required, though, to describe cardiovascular function more completely. This article describes a flow measurement system suitable for implantation purposes which can be incorporated into a multichannel system for simultaneous measurement of other parameters such as pressure and ECG.

Both the ultrasonic and electromagnetic techniques were considered for this design. Although the ultrasonic is probably more amenable to low power operation, the electromagnetic technique was selected because of its accuracy, reliability, and wide acceptance. The electromagnetic technique has a 30-year history of development and refinement so that its accuracy, limitations, and modes of application are well understood (2). Conversely, the more recent ultrasonic technique shows great promise, but requires

further development. Theoretical and experimental research continue to determine whether Doppler, pulsed Doppler, or pulsed time is most suitable for cardiovascular applications and to determine the levels of accuracy to be expected under various physiological conditions. The electromagnetic system was selected since the purpose was not to do an exhaustive research on flow techniques, but to design a practical, accurate, low powered instrument for immediate laboratory use. The design to be described represents an effort to reduce the power requirements of an electromagnetic flowmeter to its absolute minimum, consistent with accurate operation.

SYSTEM DESIGN

The essential elements of an electromagnetic flowmeter system are shown in Figure 1. Signal conditioning, such as preamplification and

Fig. 1. System block diagram for electromagnetic flowmeter.

demodulation, can usually be accomplished at the microwatt level with currently available transistors, so any design to lower power consumption must concentrate on reducing the many watts of power normally used in the field coil. The square-wave (3) type of magnetic coil excitation was selected instead of other methods, such as sine-wave or gated sine-wave, because it is the technique most amenable to low power operation. Also this type of modulation appears to provide the best potential for accurate zero flow determinations.

The circuit diagram of a low powered, battery operated system is shown in Figure 2. The primary power source is a pair of NiCad rechargeable batteries. These batteries can be periodically recharged while implanted via an inductive pick-up coil (4). The transducer field coil is alternately connected by transistors Q_{26} and Q_{27} to the ± 1.4v battery potentials. The current drain is dependent upon the transducer impedance with typical values of 2 to 3.5 ohms for the 8mm to 2mm flow cuffs, respectively. Transistors Q_{26} and Q_{27} provide extremely low internal impedances so that for currents up to 1 ampere, the internal voltage drop is less than O.1v. Under load the batteries normally run at 1.2v so that currents of 0.3 to 0.5A are required from the battery. The two penlight-size batteries used are rated at 0.5A hours. For a 0.3A peak current, the average current will be 0.15A, since each cell is only loaded half the time. Typical operating periods of two to three hours without recharging is then possible. A square wave frequency of approximately 300Hz is used for the field coil excitation.

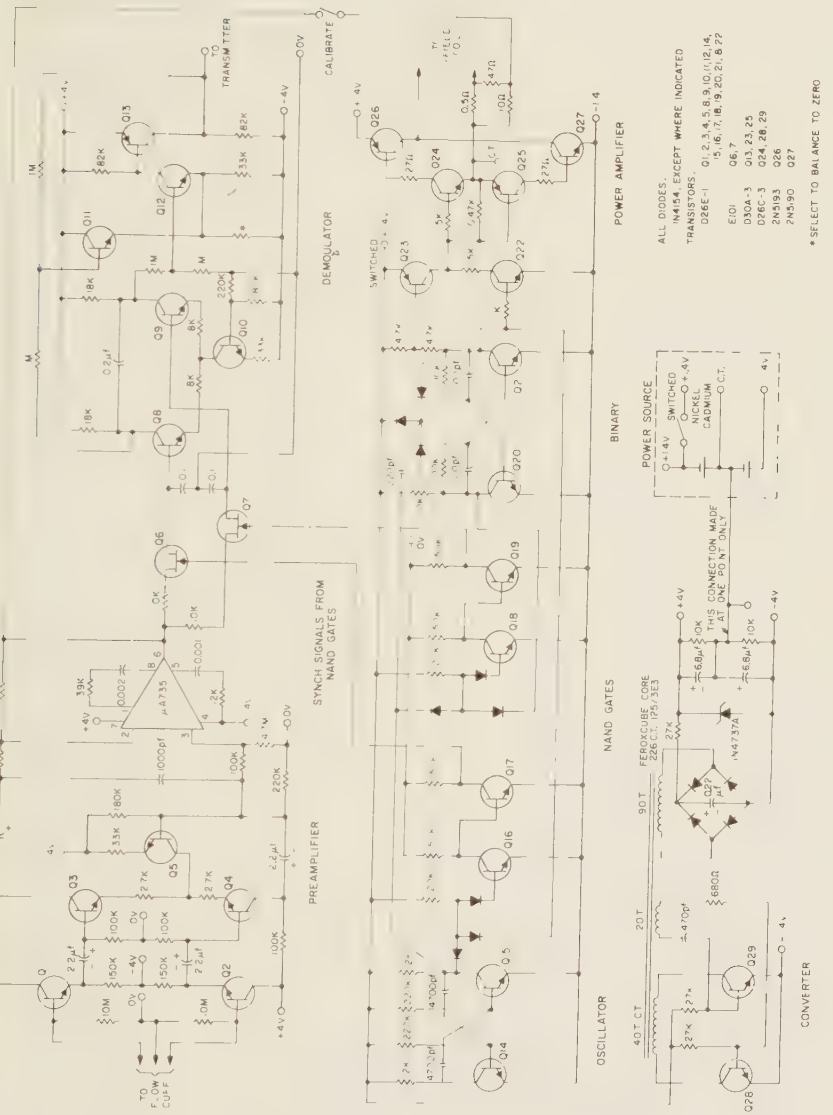

Fig. 2. Low power electromagnetic flowmeter circuit diagram.

A highly efficient field coil excitation is possible by the use of transistors having very low forward impedances of less than 0.1 ohm, and operation in a switching mode where the transistor is either saturated on or completely off. The power loss in the transistors is less than 10% of the power delivered to the field coil. Efficiencies of 90% or better are possible with a square-wave system while other systems such as a sine-wave would result in efficiencies of less than 50%. Additionally, it should be noted that the battery is switched directly across the field coil so the coil impedance must be designed to provide the desired field strength (ampere-turns) with the potential of one battery cell. Most electromagnetic flowmeters use a constant current source to maintain essentially a constant field strength. Although this is convenient for calibration purposes, it is not essential and is not suitable for the high efficiency needed in this design. Since the battery voltage will change slightly, depending upon its charge condition, and the coil impedance will change with temperature, a measurement of the field current is required in order to properly calibrate the readout data. A 0.5-ohm resistor is used in series with the field coil and connected to the demodulator input to measure the field current when calibrations are to be made.

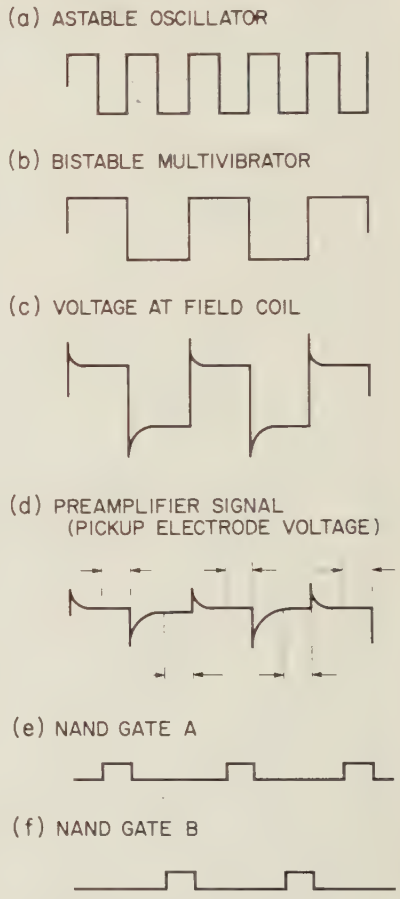

Fig. 3. System waveforms.

The system waveforms are shown in Figure 3. The values shown in Figure 2 for the astable multivibrator, Q_{14} and Q_{15}, provide an oscillation frequency of 600 Hz. This is divided by binary Q_{20} and Q_{21} to obtain a 300 Hz square wave that drives the power amplifier. This arrangement offers a number of advantages: First, a symmetrical square-wave is available for the power amplifier without critical component adjustment. Second, a combination of the 600 Hz and 300 Hz in two nand gates produces the gating signals needed in the demodulator. The FET gates, Q_6 and Q_7, are turned

on only during the last half of each square wave excursion as shown in Figure 3. This allows ample time for the switching transients to disappear. The switching transients will cause zero errors if they have not returned to zero by the time gates Q_6 and Q_7 are turned on. An air-core type of transducer is used so that the transient will rapidly die out and not affect instrument zero.

As seen in Figure 1, amplification and demodulation of the low level electrode signals is a major aspect of an electromagnetic flowmeter system. Although this signal conditioning can be accomplished at very low power levels, its design is quite critical, since the electrode signals are in the microvolts. The Zepeda transducer (Zepeda Instruments, Seattle, Washington) being used is designed to operate at 1 ampere in the field coil. The power source described typically provides an average current of 300ma; as a result the pick-up signal will be proportionately smaller. With an 18mm cuff on the ascending aorta and a flow velocity of 120 cm/sec, signals of approximately 25 to 30 μV are obtained. This low level square-wave signal must be amplified and demodulated to provide an analog output. Q_1 and Q_2 provide a high input impedance followed by amplification in Q_3 and Q_4 and the UA735 amplifier. The amplifier is AC-coupled and has a gain of 1000. Low frequency response is provided to preserve the 300 Hz square-wave. The resultant 25-30 mV square-wave signal is applied to switching transistors Q_6 and Q_7 for demodulation. As shown in Figure 3, the transistors Q_6 and Q_7 are gated "on" only during the last half of each positive and negative excursion. The balanced arrangement of Q_6 and Q_7 eliminates the common mode signals, such as electrode polarization potentials, and demodulates the carrier induced waveform. A differential DC amplifier provides a low impedance, single-ended analog output.

A breadboard assembly of the components of the circuit of Figure 1 is shown in Figure 4. Although the total number of individual components exceeds fifty (50), the total system size can be very small, since careful consideration is given in the circuit design to specifying only electronic components that are physically very small. (The small size of the transistors, about the size of a pinhead, should be noted). The power transistors required to control the field current are somewhat larger. The resistors are about .072" diameter by 0.15" in length. The number of capacitors required are kept to a minimum, and except where essential, only values less than a few thousand picofarads are used. Figure 4 is a test circuit where the parts are spread out for easy testing. In the final packaging a volume of less than 10 cm^3 is required for all the electronic components.

RESULTS

A typical recording from an awake, unanesthetized dog, three weeks

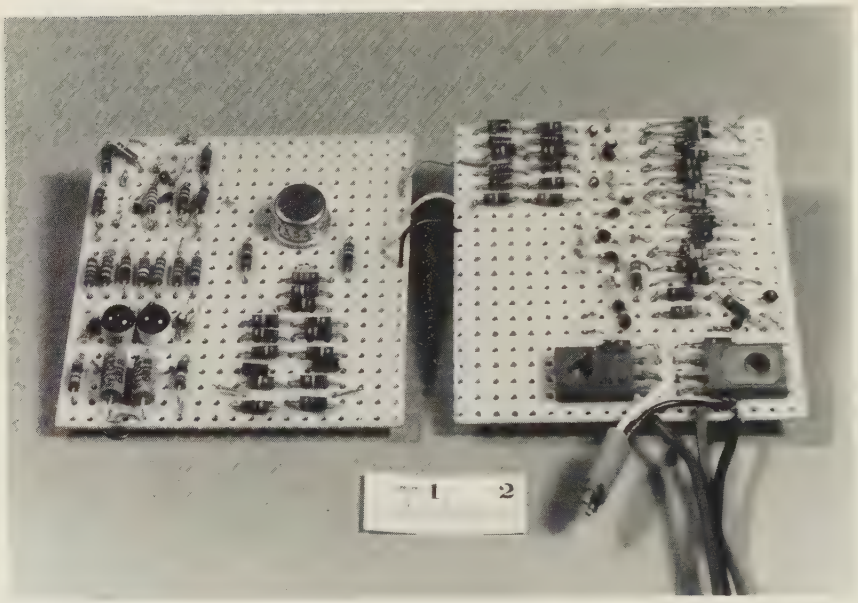

Fig. 4. Electronic assembly of the circuit in Fig. 2.

after implantation, is shown in Figure 5. This recording is taken from the descending aorta. Since the field coil is operated considerably below its rated 1A level, the noise level is slightly higher than might normally be expected. Figure 6 is a recording from the ascending aorta and the noise disturbance from the ECG is considerably more pronounced. If the field coil is operated at a higher current level, the ECG disturbance would be proportionately reduced, but at a sacrifice in power consumption. The more remote a flow probe is from the heart, the more minimal the effect from the ECG.

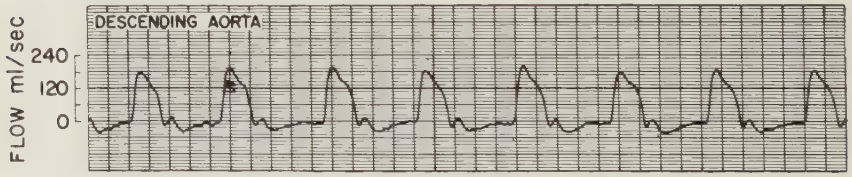

Fig. 5. Decending aorta recording of a dog.

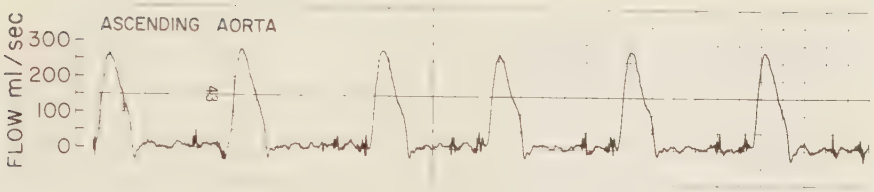

Fig. 6. Ascending aorta recording of a dog

SUMMARY

This design shows how an electromagnetic flowmeter system can now be made small enough and sufficiently low powered for total implant applications. The signal conditioning to obtain an analog voltage output is described. This must be combined with a suitable telemetry system for implantation. In order to measure other important physiological variables, such as pressure and ECG, the flowmeter should be made a part of a multiple-channel telemetry system.

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6. FABRICATION OF CONTINUOUS WAVE ULTRASONIC DOPPLER FLOW TRANSDUCERS FOR CHRONIC IMPLANTATION[1]

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The ultrasonic Doppler method for measurements of peripheral blood flows in chronic animal preparations is attractive on a number of bases. Aside from the provision of a measure of volume flow under most physiological circumstances, the inherent stability of the Doppler flowmeter, and its suitability for radiotelemetry, the physical and electrical characteristics of the Doppler flow transducer are particularly suited for long term measurements in chronic animal preparations. The cylindrical transducer is lightweight: it has a net specific gravity of approximately 1.0. It is fabricated from a plastic which usually causes only a transient inflammatory response. The transducer body is sufficiently strong to withstand the trauma of surgical implantation and, once implanted, can be expected to last indefinitely without mechanical deterioration. The transducers are capable of fabrication by relatively unskilled but meticulous workers at a relatively low labor cost per unit. In addition to the attractive mechanical and economical features of the Doppler flow transducer, the electrical characteristics of the transducer are compatible with long term implants in the harsh environment of the biological tissues. The piezoelectric crystals used in the Doppler flow transducer are operated at resonance. Their impedance at resonance ranges from 50-200 ohms. This feature allows the use of relatively poorly insulated, twisted-pair wire with the consequent advantage that the insulation can deteriorate appreciably before the electrical shunting of tissue fluids will significantly influence the flow signal. Over the number of years that this instrument has been used in our laboratory we rarely have had a premature failure. The transducers function routinely for at least six weeks using copper wire leads, and the life of the transducer can be extended considerably by the use of stainless steel wire.

With all of these attractive features a number of investigators who have

[1]Supported, in part, by USPHS NIH Grants HE 13441 and HE 12373.

attempted to use the Doppler flow system for chronic animal experiments have reported dissatisfaction with many of the commercially available transducers: the transducer shells are quite fragile and fracture during implantation, or they fail electrically within a few days following implantation. These difficulties can be overcome by proper design and fabrication of the flow transducer. The following is an informal relation of how we arrived at the current transducer design and a recipe for fabrication of the transducers we have used for a number of years.

DESIGN CRITERIA

The original transducers were designed largely on an empirical basis. The available information regarding the interaction of ultrasound with the erythrocytes would not allow precise theoretical prediction of optimal operating frequency. The first Doppler ultrasonic flowmeter used successfully for blood flow measurements used 5 MHz because we expected the backscattered energy to be some direct function of frequency, and the highest frequency piezoelectric crystal available in 1957 was 5 MHz. Since that time we have conducted an empirical evaluation of 5, 7, 9 and 11 MHz and have found nominally 9 MHz to be a reasonable compromise between ease of transducer fabrication and signal-to-noise ratio for measurement of flow through peripheral vessels. We have used 9 MHz since 1966. For large vessels or for transcutaneous applications where one is interested in visualizing deep vessels, i.e., greater than 2 cm, attenuation considerations would indicate lower frequencies, i.e., 3-5 MHz.

Another design consideration involves the selection of an optimal angle between the acoustical axis and the flow axis. Initially, it was expected that there would be an optimal angle for maximal backscattered energy. We felt intuitively that the magnitude of the backscattered energy would be blood velocity (erythrocyte orientation) dependent. Nevertheless, the angle selected for the first transducers was based solely on geometrical considerations. Since a variation in angle between the acoustical axis and the flow axis will influence the sensitivity to frequency shift per velocity increment of the instrument, the angle of 45° was selected to minimize this effect. Since that time we have found that if there is a relationship between the orientation of the red cells and the magnitude of the backscattered signal, it is not sufficient to preclude the accurate measurement of velocity. Our experiments have not been sufficiently systematic to exclude or to quantify the velocity dependence of the magnitude of the backscattered energy, however.

Two other factors enter into the selection of the angle of the crystal for a particular application. One is the length of the transducer such that it will fit between branches of the blood vessel, and the second is the point or volume within the cylindrical transducer from which the flow information is derived. The red cells moving within the prismatic volume common to both the emitting crystal field and the receiving crystal field are measured. In other words, the velocity of the red cells moving at the intersection of the two fields is measured. If the two fields intersect at a point beyond the transducer body, the assumed constant relationship between measured velocity and desired volume flow may be distorted. Note that the relationship between measured velocity and volume flow is constant only so long as the cross-sectional area is constant. We assume that the rigid cylindrical transducer holds the blood vessel lumen constant. For this reason, the angle of the crystals is selected such that the acoustical axes intersect within the lumen of the transducer at the far end of the transducer. For most applications the angle is 45°.

Since the crystals are at an angle with the blood vessel there must be "side arms" on the cylindrical transducer to hold the crystals. In general, the transducer should occupy as little space as possible, therefore the side arms should be short, i.e., one edge of the crystal should be in contact with the blood vessel wall. On the other hand, intuitively it seems that one would like to have a uniform field within the blood vessel, i.e., one would like to radiate the blood with the far field of the crystal. For a practical transducer, this would require side arms approximately 2-4 times the diameter of the blood vessel. We have sacrificed uniformity of field with its theoretical advantages for minimum transducer size. The crystals are mounted within the plastic cylinder such that the edge of the rectangular crystal is as close to the blood vessel wall as possible but still supported by the body of the transducer, i.e., the sharp edge of the crystal does not come in contact with the blood vessel wall. For some applications it may be desirable to move the crystal back from the blood vessel such that the vessel is radiated with a uniform field. This remains to be studied.

What should the shape of the crystal be? For reasons of crystal Q, acoustical field uniformity, and suppression of spurious modes of crystal vibration, one would select a circular plate. In the practical situation we have found negligible difference between circular plates and rectangular plates. The rectangular plates are far less time consuming to cut than are the circular plates. A systematic study to determine the optimal relationship between major dimension of the crystal and the blood vessel diameter has not been conducted. For transducers with lumen diameters of 5 mm or less, the diameter of the crystal equals the transducer lumen diameter. For larger

transducers the crystal diameter is approximately two-thirds the transducer lumen diameter. The largest crystal we use is a rectangle, 10mm x 5mm. The smallest transducer which we have used routinely is 4mm lumen diameter. In exceptional cases, we have used transducers with 2mm lumen diameters. Signal-to-noise ratio of the acoustical signal is excellent in these tiny transducers. Still, for chronic animal work one can't help but wonder the extent to which encircling a 2mm blood vessel with a plastic cylinder, and the accompanying transducer wires, can be expected to modify the variable one is attempting to measure. For this reason, we have confined our attention to relatively large (4mm) blood vessels for routine chronic animal work.

MATERIALS

The ideal piezoelectric material would be a low noise, highly efficient, high Q electromechanical transducer. Quartz immediately comes to mind. The high driving voltages and high impedance of quartz with the associated requirements for electrical shielding and insulation almost preclude quartz as a routinely used, chronically implantable material for transducers. Indeed the availability of the synthetic piezoelectric (ferro-electric) materials in the 1950's (barium titanate) made the chronic implantation of acoustical devices practical on a routine basis. We initially used barium titanate but changed to lead zirconate-titanate when it became available. A significant advantage of lead zirconate-titanate is its higher Curie temperature (approximately 300°C). This reduces the probability of depolarizing the material when soldering wires to the electrodes.

Obtaining high quality piezoelectric material in a reasonable delivery time has been a real problem over the years. Examples of the difficulties with large, reputable companies are: over one year delivery time after the receipt of the order, air bubbles in the plates, gross differences in electrical characteristics from order to order, gross variations in the bonding of the electrode to the crystal material, etc. While many commercial firms may currently provide adequate materials in reasonable times we have used the materials provided by Transducer Products, 95 Wolcott Ave., Torrington, Conn. 06790, since 1966. We order stock plates for flow transducers as follows: 1 inch squares of LTZ-5, thickness resonance at 9 MHz, plus or minus 5%. Silver electrodes to edge. These cost $20 to $30 each, depending upon the quantity ordered.

The transducer body consists of two plastic hemi-cylinders with depressions to house the piezoelectric crystals. These were initially made from methylmethacrolate or epoxy. When using these transducers on the coro-

nary artery or femoral artery, acoustical reflections from adjacent structures interfered with the signal backscattered from the red cells. On the femoral artery the spurious signal was particularly apparent when the animal moved. On the coronary vessel, there was an interfering signal synchronous with artial contraction. It appeared that the sound was passing not only through the blood vessel wall into the blood vessel but was also being coupled through the transducer wall to strike adjacent structures which reflected sound back to the receiving crystal. The signal backscattered from the erythrocytes is very small such that the signal reflected from the moving structures around the transducer gave rise to a spurious flow signal. In other words, it is desirable to make the transducer body of a material that is essentially opaque to ultrasound. We currently mold the transducer body using expandable polystyrene beads, Dylite F-40-C, obtained from Sinclair-Koppers Co., Koppers Building, Pittsburgh, Pa. One can obtain polystyrene expandable beads which contain a fire retardant. We found that some fire retardants are toxic, i.e., when flow transducers fabricated from polystyrene beads containing a fire retardant were implanted around the coronary vessels of baboons, there was continuous growth of connective tissue such that the vessels occluded in approximately four weeks.

The most common reason for failure of a Doppler flow transducer is wire breakage. It would seem that the amount of work that has gone into development of pacemaker leads would have provided a solution to this problem. In our experience, wires provided for pacemaker leads are too stiff, too large, or, at least as important, much too expensive. (We were recently quoted a price $30/3 ft. length, single conductor, of what appeared to be superb wire for our application. Since our experiments commonly involve the implantation of 10 different piezoelectric plates involving 20 individual wires, the price per animal for wire was prohibitive.) We currently use a multistrand copper, PVC insulated wire that is sufficiently corrosion resistant to last the duration of most of our experiments, i.e., 2-3 months. We order this wire as follows: 2 conductor, AWG29, Str. 51/46, Spec 3006-023-29-11, type B.C., Calmont Wire and Cable, Inc., 420 East Alton St., Santa Ana, Calif., 92707. (Specify insulation color). Its current price is approximately $100/1000 ft. For longer term experiments we use a multi-strand stainless steel wire available from Konigsberg Instrument Co., 2000 East Foothill Blvd., Pasadena, California, 91107.

The primary difficulty with the stainless steel wire is the difficulty in soldering the wire to the electrode. This will be discussed later. Some of the stainless steel wire we have used has had a tendency to migrate. In one experiment with sled dogs where a relatively long postsurgical retraining period was involved, we left the ends of the transducer wires buried

subcutaneously between the scapulae over a period of approximately six weeks. We found that some of the stainless steel wires had migrated back to the abdominal or thoracic cavities and were unavailable. When one buries stainless steel wire subcutaneously expecting to retrieve it at the time of the experiment, it is wise to anchor it in situ with a suture. Another difficulty with the stainless steel wire currently used is that the insulation is not color coded, i.e., identification of leads is a bother.

We insulate each crystal, after having attached the wires, with a dilute solution of "Insl-X". (Insulating tool dip, E-33 clear, Insl-X Products Corp., Yonkers, New York.) We do not know the precise composition of this substance. It was brought to our attention years ago by neurophysiologists who used it to insulate metal microelectrodes. They found that it formed a thin, highly insulating film without cracks. We began using it on crystals in 1955 and it seemed effective for short term insulation of crystals. Whether it is truly an effective insulator after six weeks in an animal, and whether this insulating procedure really contributes materially to the success of these transducers, we don't know. We continue to use this procedure on the basis that it would take too long for a systematic determination of its efficacy. We suspect that one day someone may determine that dipping the crystals in Insl-X has merely ritualistic values where the transducers are to be implanted for a long term period.

We commonly use standard 60/40 solder. We have a feeling that solder with 2% silver content makes the soldering task a bit easier. Low melting temperature solder would be desirable. We don't use it. We have tried conductive epoxys and found them to be too time-consuming and the final joint is not all that reliable.

Where epoxy is called for we use Hysol Epoxy Patch Kit, 1C white.

TRANSDUCER FABRICATION

The major impediment to in-house fabrication of Doppler flow transducers is the availability of the molds for molding the transducer bodies. The molds are reminiscent of the ones developed by Nolan Watson when we worked together on the pulsed ultrasonic flowmeter at the University of Washington. The current molds are all metal, they are fairly complex to machine, and only one-half the flow transducer body can be molded at a time. The cost of tooling up for high-speed mass production molding of transducer shells is prohibitive for our application but certainly is feasible. Our molds are available for your inspection in our laboratory at your pleasure. We would be happy to send very small numbers of the molded plastic hemicylinders to bonafide users as they are available from our lab,

i.e., if we have any left over when you happen to write. The pressure cooker we use is a 6 qt. home model. It has a pop-off pressure of 15 psi. Since we have extremely hard water in San Diego, we use distilled water to prevent accumulation of deposits on the mold.

The crystals are cemented into the transducer shells using a polystyrene solvent glue, i.e., Q-dope, available at general electronics stores. Q-dope is also used to fasten the fabric hinge to the transducers. The hinge material is Dacron cut from worn out wash-and-wear white shirts. A large rectangle is cut from the shirt and painted with Insl-X and allowed to dry. This serves as stock from which the hinges are cut. One-eighth inch umbilical tape is used for the ties for large transducers. Surgical silk is used for the small transducers.

A mold release agent is used to minimize sticking of the resultant molded part to the mold. While expandable polystyrene beads do not usually stick to the mold, an occasional application of a mold-release agent is helpful. Wiping the inside of the mold with a silicone lubricant is adequate. The mold is then dry wiped clean to leave only a very thin film of the lubricant on the mold. The two halves of the mold are held together in the hand and the mold is filled with the polystyrene expandable beads. Tap the mold gently while filling to completely fill the mold. The hardness of the resultant transducer half will in part depend on how full the mold is. The mold should be sufficiently full that a good bit of force is necessary to force the filling hole plug into the filling hole, i.e., the beads should be initially compressed by the filling hole plug. The filling hole plug is clamped into place with the screw which also holds the two halves of the mold together. The filled mold is placed in the pressure cooker which is then brought to 15 psi. Fifteen minutes at this pressure insures complete expansion and fusion of the polystyrene beads. If an inadequate cooking time is used, the resultant shell will appear adequate but the beads will not have completely fused. The resultant flow transducer will be fragile. A number of the commercially available flow transducers apparently suffer from this difficulty and break during implantation of the transducer. The mold is removed from the pressure cooker, and allowed to cool. The plastic shell will usually adhere to the male part of the mold. A flat razor blade is inserted between the transducer edge and the mold and the transducer usually pops loose. Take care not to scratch the brass mold with the razor blade. A redesigned mold would include a pin to force a molded piece out of the mold without resorting to the razor blade procedure. This molding process is quite time-consuming, the minimum cycle time being on the order of 20 minutes.

The flashing and sharp edges of the plastic shell are removed using a

razor blade and sand paper. The holes through which the wires pass are drilled open.

CRYSTAL PREPARATION

The crystals are cut from the stock material to a size to fit the cavity in the transducer body. A number of approaches have been suggested and utilized. Commonly these involve the use of diamond saws or jets of air carrying a cutting compound. We have found these approaches to be relatively expensive and time-consuming. We cut the crystals in a way analogous to the way one cuts glass. The one inch stock crystal is marked according to the size of the resultant crystals desired, e.g., 1 cm x 0.5 cm marks are put on the crystal blank. The crystal square is placed on a clean flat surface, e.g., a piece of plate glass. A small steel straight-edge is laid along the line where the cut is desired and held firmly in place with finger pressure. The tip of a sharp # 11 scalpel blade is run firmly along the edge of the straight-edge to scribe the crystal. A crystal plate is then broken along the scribed line by holding the crystal between the fingers and applying bending force. It might seem easier to simply apply pressure to the crystal with the scribe line overhanging the straight edge but we have found greater success with simply picking the crystal up and breaking it along the line, attempting to keep the pressure on both sides of the scribed line constant along the crystal. A little experience and judgment is involved in this procedure to the extent that one can expect to ruin the first few cuts. In the long run the procedure is far faster and more economical than the other approaches. The sharp edges of the transducer are smoothed by sanding or filing. Where rounded crystals are desired, careful cutting with a small pair of sharp side cutters or, better, a pincer type fingernail clipper can be used to nip small pieces away from the edge of the crystal and thus bring it to the desired form.

Two wires are soldered to each crystal. Place the cut crystal into the plastic transducer half to get an idea of where the wires should be attached to the crystal. Using a dull knife tip, burnish the small electrode area where the wire is to be attached. Wipe a minute amount of non-corrosive soldering paste on this burnished area. Using a clean, low wattage soldering iron (20-30 watts) carrying a thin film of solder on the tip, touch or wipe the burnished area of the electrode with the tip of the soldering iron. A very thin film of solder should be left on the electrode. This also takes a bit of practice. The wire is prepared by stripping approximately 2mm of insulation away from the wire, taking care not to cut the strands of wire. A "hot wire stripper" is helpful. Twist the bare wire between the fingers to make it

round and bring the strands together. Tin the bare wire. The tinned wire is then cut to expose about 1mm of bare wire. The twisted-pair wire is then bent and twisted such that the two bare ends of the wire are opposed and separated by a space approximately equal to the width of the crystal. One of the bare wires is placed in contact with the tinned area on the crystal. The clean soldering iron is placed on top of the tinned wire until the solder on the wire fuses with the solder on the crystal. This also takes a bit of experience and practice. One commonly leaves a great blob of solder on the crystal during this step but one quickly learns to fuse the solder leaving a minimum of solder on the crystal. The same procedure is used to connect the other wire of the twisted pair to the other side of the same crystal. If one takes excessive time with too hot an iron in soldering on the second wire, the temperature of the crystal will rise, the solder of the first wire will melt, and the wire will come off. Practice will overcome this difficulty.

Where a stainless steel wire is to be used the procedure is somewhat different and more tedious. The main difficulty involves tinning the stainless steel wire with solder. A stainless steel acid flux is used (All State "Duzall"). The insulation is stripped from the tip of the stainless steel wire in the same manner as the copper wire. Care is taken not to crimp the stainless steel wire or the individual strands will separate. A reservoir or bubble of solder is carried on the tip of a hot soldering iron. The bare stainless steel wire is dipped alternately in the stainless steel flux, then into the solder. Protect your eyes from the fumes generated by this stainless steel flux. After repeated immersions the solder will adhere to the stainless steel wire. Following this tinning procedure, the acid flux is washed from the wire with water.

After the wires have been attached to the crystals, the crystal is immersed slowly in Insl-X diluted with toluene to a watery consistency. The goal of this is to form an extremely thin coating of Insl-X over the crystal and solder joint up onto the insulation of the wire. After the Insl-X has hardened (a few minutes) one should see a glossy film of Insl-X on the surface of the crystal viewed in reflected light. There should not be a thick coat of Insl-X remaining on the crystal. If there is, the solution is not sufficiently dilute.

FINAL TRANSDUCER ASSEMBLY AND TESTING

After the Insl-X is dried, the crystal wire combination is glued into the plastic shell. The wires are drawn through the hole which has been drilled in the shell and the crystal is fitted into the cavity in the shell. A thin film of Q-dope is painted on the crystal around its perimeter and the crystal is held in position within the shell for a few minutes until the Q-dope hardens

slightly. The crystal-transducer combination is then hung up to dry overnight. Before final gluing of the crystal into the shell with the Q-dope, the crystal is placed in position and the wires are given a bend to take the strain from the crystals. Neither the solder joints nor the Q-dope are mechanically strong and are not relied upon to withstand force.

Each transducer half is then tested for electrical activity and the approximate resonant frequency is measured. The leads from a crystal are connected to the output of a signal generator (Hewlett Packard 606-A) providing a variable frequency signal with a constant amplitude of approximately 4v peak to peak. The transducer is immersed in water about 1cm below the surface and the crystal is oriented to direct the acoustical beam to the surface of the water. A lamp is situated to reflect the light from the surface of the water overlying the crystal to the observer's eye. As the frequency of the signal generator is varied through the resonant frequency of the crystal, the acoustical field will elevate the surface of the water and this elevation can be seen in the reflected light. This elevation can be exaggerated using a fluid with a lower surface tension, e.g., alcohol, and it can be more easily seen in reflected light if viewed against a dark background. The existence of this dimple indicates that the crystal was not completely depolarized and the electrical wires were not shorted together during the soldering process. Center frequency of the crystal can be approximated by noting the frequency at which the maximum elevation of the water surface occurs. This frequency is noted for each transducer half. It can be expected to have a range among transducers of as much as 200 KHz with a 10 MHZ crystal. This probably occurs because the solder left on each crystal is not precisely the same in amount or in area of deposition. This is a crude but effective quality control procedure. A number of transducer halves are made at the same time and the transducer halves are paired to make the projecting and sensing crystals of a completed transducer as nearly equal in frequency as possible.

Final assembly of each of the pairs of halves involves fastening the hinge and the suture material and finally bonding the wire and the suture to the body of the transducer using epoxy. A rectangle of the Dacron hinge material is cut to a length just shorter than the length of the transducer, and to a width such that the hinge will cover approximately one-third of each transducer half. The two halves are mated together and clamped in this position in a vise. The hinge material is coated with Q-dope and pressed into place to serve as a hinge between the two halves. There is a tendency to glue the two halves of the transducer together permanently during this procedure. The suture, either 1/8" umbilical tape for large transducers or surgical silk for small transducers, is tied around the transducer in the same manner that it will be tied around the transducer during implantation. The

length of the suture should be at least 2 ft. Suture material is cheap and the surgeon will be attempting to tie the two ends together at the bottom of a cavity. You can simplify his problem by making the sutures overly long. Epoxy is coated over the electrode wires and the suture, to bond the wires and suture to the body of the transducer. The wire exit hole from the transducer is filled with epoxy. The epoxy should be placed to eliminate sharp edges from the final structure. The epoxy bond serves as the major stress-bearing material since the Q-dope does not make a sufficiently strong mechanical bond.

SUMMARY

The published calibrations verifying the linear relationship between that which the Doppler flowmeter measures and volume flow have been conducted using transducers fabricated according to the above procedures. In the above discussion we have assumed the reader has general familiarity with the principles of operation of the Doppler flowmeter and the general form of the transducers. The articles cited below which describe the Doppler flowmeter and its applications may be of help to the reader. The circuit diagrams of the Doppler flowmeter and readout system we currently use are freely available to those who request it.

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7. CALIBRATION OF THE ULTRASONIC DOPPLER FLOWMETER IN SITU[1]

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The utility of the continuous wave ultrasonic Doppler shift blood flowmeter (1, 2) has been demonstrated in a variety of experimental situations. Its suitability for telemetry of measurements of blood flow in association with arterial pressure has enabled studies in non-docile animals, e.g., coronary flow in baboons (3), carotid flow in giraffes (4), and studies of near maximal exercise in unrestrained dogs (5, 6). The mechanical and electrical features of the Doppler transducer discussed in another section of this Symposium (7) enable routine three-month operation before transducer failure in chronic animals. Thus, within-animal comparisons of normal and induced disease states such as complete heart block (5, 8), severe anemia, and congestive heart failure (9) are possible.

The continuous wave ultrasonic Doppler shift blood flowmeter utilizes the Doppler principle whereby sound reflected from a moving target will be shifted in frequency by an amount proportional to the target velocity. For blood flow measurement, 9 MHz sound is beamed through the unopened blood vessel wall into the bloodstream. The sound is scattered isotropically, primarily by the erythrocytes, and a fraction of the backscattered sound travels through the blood vessel wall where it is sensed. The backscattered sound differs in frequency from the incident sound by an amount proportional to the blood velocity, in accordance with the Doppler equation which states that the shift in frequency equals:

$$\frac{2F_t \; v \; \cos \alpha}{C} \qquad (1)$$

where F_t = incident sound frequency
v = erythrocyte velocity

[1] Supported, in part, by USPHS Grants HE 12373, HE 13441, and HL 15631.

α = angle between the sound axis and the flow axis
C = velocity of sound in blood

For a practical transducer operating at 9 MHz the Doppler shift in frequency will be nominally 100 Hz / cm / sec. The backscattered signal is mixed with the projected signal to produce the sum and difference frequency signals. The frequency of the difference frequency signal is recorded using a zero-crossing frequency meter, and calibrated in terms of instantaneous blood velocity.

Conversion of velocity measurements to those for volume flow can be accomplished using a number of approaches if vessel cross-sectional area can be assessed. This can be accomplished by measuring the external diameter of the vessel prior to original implantation and just prior to sacrifice of the animal. The vessel wall thickness can be measured at autopsy and twice this value can be subtracted from the external diameter to yield the internal diameter. A more elegant but more complicated method of assessing cross-sectional area is to use angiographic techniques which permit in vivo visualization of the internal diameter of the vessel. However, this requires elaborate radiographic instrumentation and catheterization of the animal using fluoroscopy which limits its usefulness. Once a measure of vessel diameter is obtained, calculation of volume flow is then straightforward, i.e., the product of cross-sectional area and blood velocity. However, it must be mentioned that small errors in estimating vessel diameter can occur which will result in significant errors in volume flow calculations.

A second method of calibration involves comparing the output of the Doppler flowmeter to values recorded utilizing another flow system as a standard, for instance, the dye dilution technique or the electromagnetic flowmeter. Accordingly, prior to sacrificing the animal a calibrated electromagnetic flow transducer can be placed on the blood vessel and the outputs of the two flowmeters can be compared. We conducted a study in which we simultaneously measured and calibrated regional blood flows in chronically instrumented dogs utilizing both the Doppler and electromagnetic techniques (10). These measurements were made a minimum of 2 weeks after surgical implantation. This study indicated that both flowmeters measured nearly equal changes in flow under a variety of conditions in the conscious animal (Fig. 1) and calibrated linearly when compared to a third measurement, i. e., the timed collection of blood flow with beaker and stopwatch during a terminal experiment (Fig. 2).

This latter method of calibration of the Doppler flowmeter, i.e., the timed collection of blood flow with beaker and stopwatch, is the most accurate means of volume calibration. This is accomplished in the following

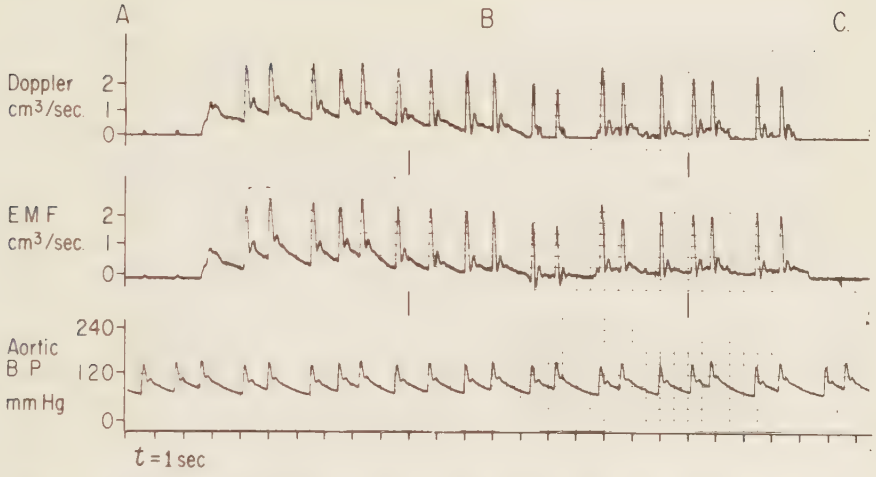

Fig. 1. Simultaneous recordings of phasic femoral blood flow with Doppler and electromagnetic flowmeters and arterial pressure. This tracing begins with an occlusive zero flow (A), followed by a period of hyperemia, then a period of reversed flow, and ends with electrical zero flow (C).

manner: The animal is anesthetized, the vessel distal to the flow probe is exposed, and its branches are tied and ligated. The vessel is then cannulated distal to the probe with an appropriately sized polyethylene tube. The deflection on the recorder is then compared to the volume of the timed collections of blood flow. Flow is varied by (1) altering resistance of the cannula with a screw clamp, and (2) altering blood flow by administration of intravenous catecholamines, carotid occlusion or hemorrhage. These calibrations are conducted at several levels of arterial pressure, including those which occurred in vivo during the course of the physiological experiment (Fig. 3). These calibrations have been employed on all major regional circulations including the coronary. In the latter case it is advisable to conduct the calibrations rapidly, since this technique necessarily interrupts the organ blood flow, which in the case for the coronary bed, may result in cardiac arrest or fibrillation.

If the animal expires prior to full calibration, in vitro techniques are available. The vessel proximal to the transducer is also cannulated. Known volumes of blood are passed through the vessel segment within the transducer either with a syringe, a pump, or an elevated reservoir and gravity flow technique.

It is advisable to pretreat the animal with heparin prior to the calibration to prevent post mortem clotting, which interferes with in vitro calibra-

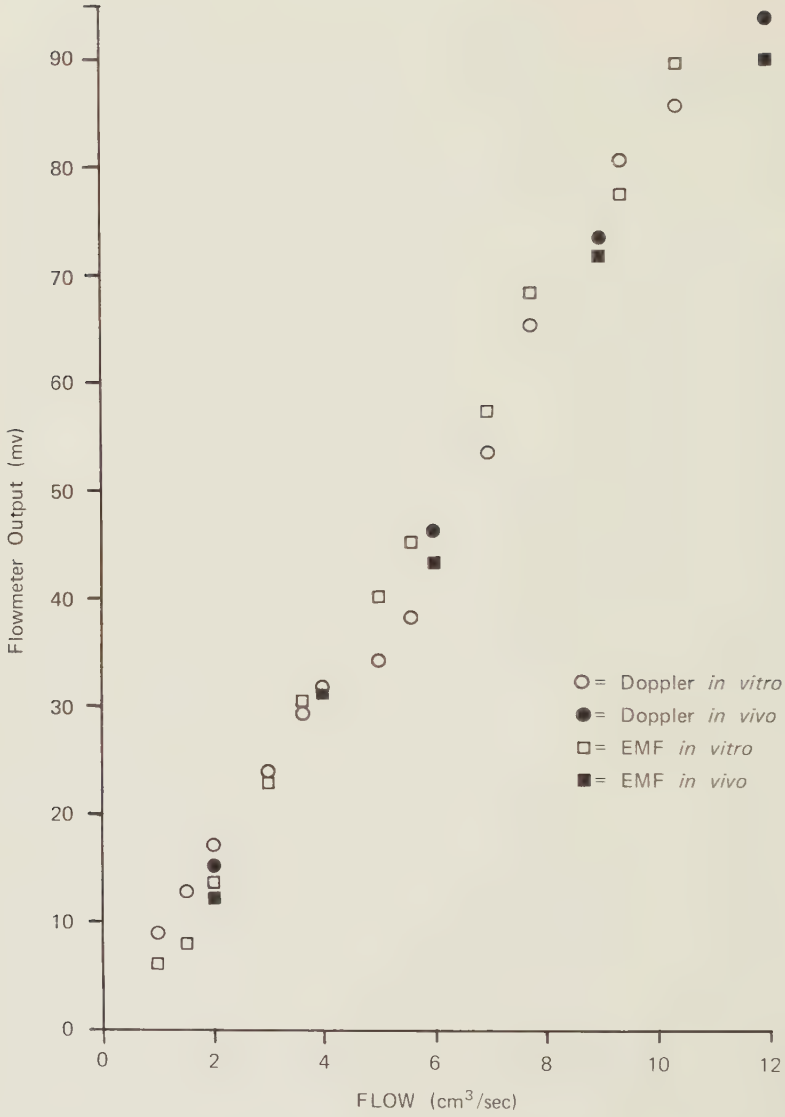

Fig. 2. Simultaneous Doppler and electromagnetic in vivo and in vitro calibrations for one animal. Abscissa represents volume blood flow. Ordinate represents flowmeter output as recorded on strip chart.

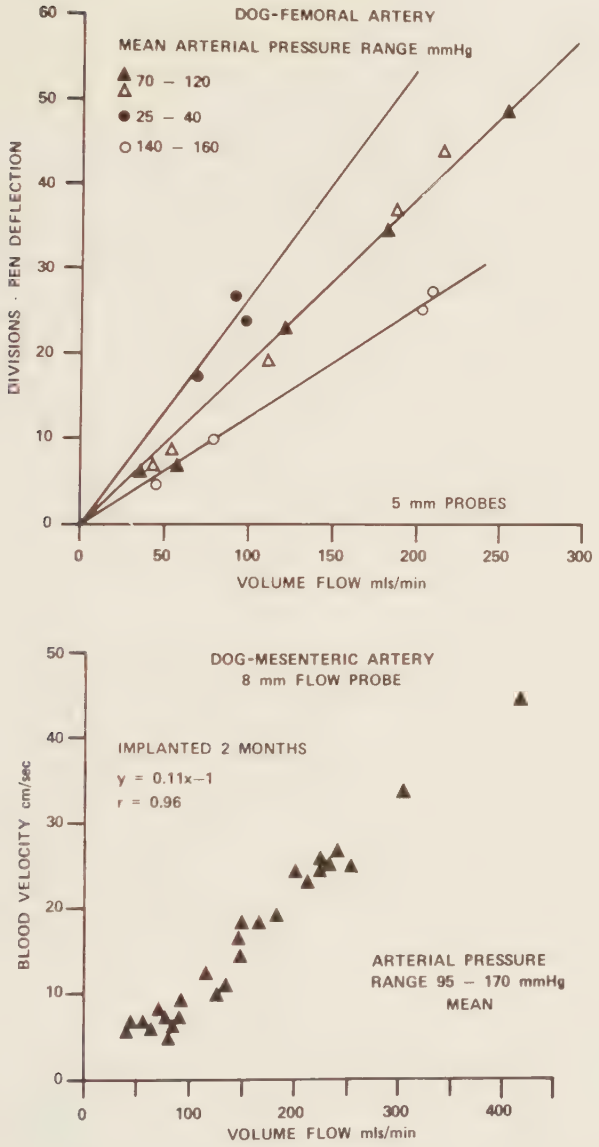

Fig. 3. Volume flow calibrations for chronically implanted Doppler flow probes on a dog's femoral artery (upper panel) and on a mesenteric artery (lower panel). The data points for flow were collected over a wide range of arterial pressures.

tion. If clotting should occur and blood is not available, another fluid can be substituted as long as it contains sufficient particles to backscatter the ultrasound. We have successfully used whole milk to calibrate the flow probes (Fig. 4, upper panels). Reliable calibrations can be obtained only if the signal: noise ratio of the flow signal is adequate. This can be assessed by displaying the flow signal on an oscilloscope, or with more experience, by listening to the audio Doppler signal. An inadequate signal: noise ratio can be confirmed by an inability to find a broad plateau in sensitivity setting of the zero crossing detector (frequency to voltage converter). In all cases, the sensitivity setting of the zero crossing detector must be within the plateau range for accurate calibrations. In the situation of poor signal: noise ratio,

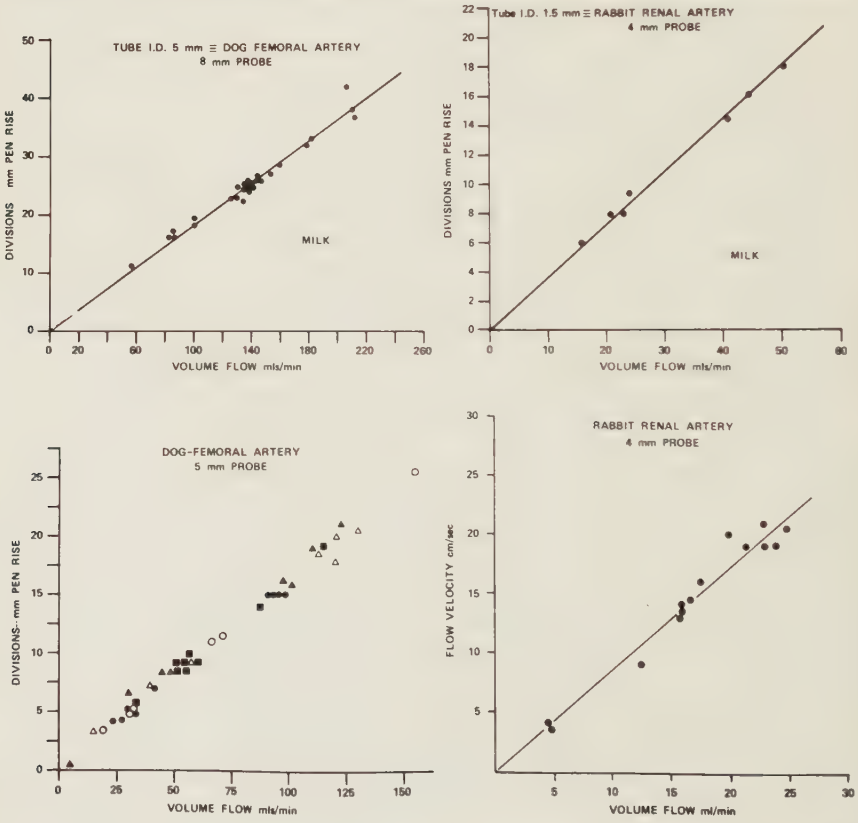

Fig. 4. Volume flow calibrations for Doppler flow probes for the dog (left panels) and the smaller vessels of a rabbit (right panels). The graphs at the top show in vitro calibrations with milk, while the graphs at the bottom show in vivo calibrations with the animal's blood.

not only are calibrations inaccurate but so is electrical zero flow reference.

A second area for cautious interpretation of Doppler flow signals and a possible source for inaccurate calibrations is the situation where an abnormal velocity profile exists. Thus in cases of turbulent flow, such as occurs distal to stenotic regions of vessels or when there is random motion of cells without net forward motions as sometimes occurs during diastole at the root of the aorta during tachycardia, the continuous wave Doppler flow system may yield inaccurate calibrations. Finally, when substantial reverse flow exists, calibration will be inaccurate. The continuous wave Doppler flowmeter is insensitive to direction of flow and records reverse flow as forward.

The techniques discussed in this paper apply to "chronically" implanted flow transducers, which have been in the animal for sufficient time to form an adherent fibrous scar to the blood vessel. This fibrous shell serves two purposes; it minimizes changes in vessel diameter with changes in perfusion pressure, and it ensures good acoustical coupling between transducer and blood vessel. In "acute" experiments acoustical coupling may be inadequate and the vessel area may change substantially with changes in pressure. Both of these effects will tend to invalidate calibrations.

SUMMARY

The techniques outlined above will yield routine and reliable calibrations of the Doppler ultrasonic flow system as long as the Doppler system itself is properly designed and properly operated. We have conducted volume flow calibrations for transducers on various sized vessels in a variety of animals. Most commonly, the peripheral vessels of dogs have been used which yield physiological flow values of 30 ml / min to over a liter / min. However, studies on smaller vessels, e.g., rabbit peripheral vessels, have indicated that accurate flow calibrations can be obtained in peripheral vessels of very small animals having flows of less than 20 ml / min (Fig. 4, lower right panel).

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8. PULSED ULTRASONIC TECHNIQUE FOR MEASUREMENT OF VENOUS FLOW

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The selection of flowmeters for the measurement of pulsatile venous flow was, in my case, influenced by contacts with Robert Rushmer and Dean Franklin. We have constructed several models of the pulsed ultrasonic flowmeter (PUFM), including a solid-state unit (1), and were the first laboratory to report simultaneous flow records from the vena cava, main pulmonary artery, pulmonary vein and aorta in an unanesthetized dog (Fig. 1) (2,3). Although we have measured aortic flow using an electromagnetic flowmeter based on a design by Francis Abel, we have used only the pulsed ultrasonic flowmeter for venous flow studies. The probes are very light, and distortion of the vessel is not a problem. The proximity of the pulmonary vein to the atrium with its large ECG signal is no problem for the ultrasonic device. The reversed flow pulses with atrial systole are faithfully recorded with the PUFM. Zero flow can be obtained by acetylcholine injection (1-3 mg, intravenously), which produces transient cardiac arrest, or by an occluder (Fig. 2) (4); this is less convenient than electronically determined zero flow but since there is little drift, frequent zero determination is rarely an important consideration.

Calibration may be performed in the same manner as for other flowmeters. Flow through a severed or cannulated vessel may be collected in a graduated cylinder and timed with a stop-watch. For aortic or pulmonic root flow, cardiac output may be obtained by dye-dilution curves, and the average stroke volume determined by dividing the cardiac output by the heart rate for the period of the dye-dilution curve. Superior or inferior vena caval flow calibration may be done without terminating the animal by inflation of a catheter-mounted Fogarty balloon at the atrial-caval juncture; the resulting change in aortic or pulmonic flow in the first few seconds, before reflex loops can be completed, will give a reasonably accurate assessment of the occluded caval contribution.

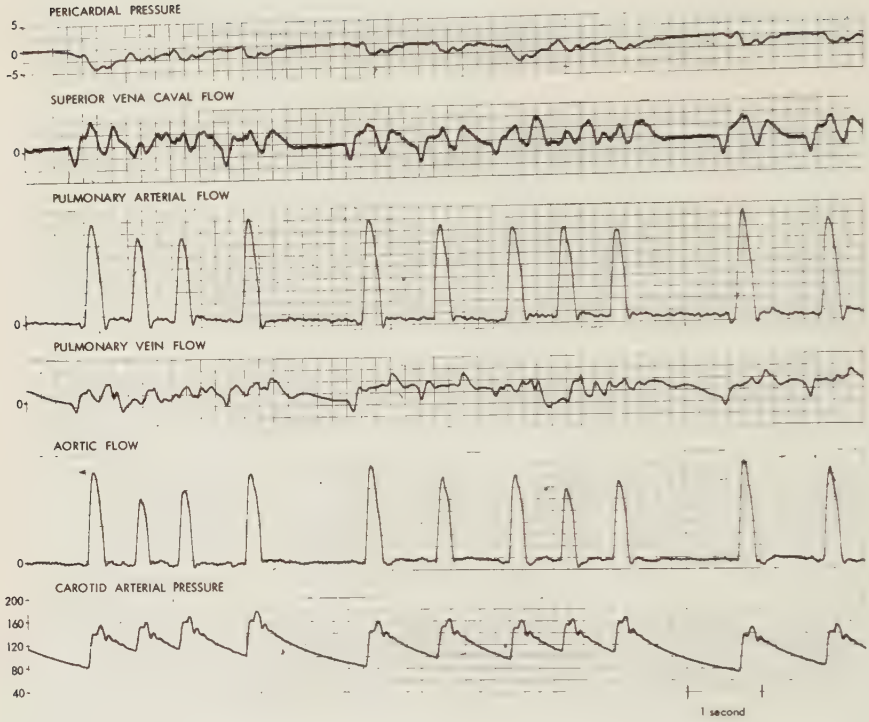

Fig. 1. Record of simultaneous pulsatile flow in the cava, pulmonary artery, pulmonary vein, and aorta in a healthy dog. Sinus arrhythmia is present, and the respiratory rate is slow. In this state, the stroke volume of the right and left ventricle are in phase, since the dominant determinant is filling interval. Reproduced, by permission, from *Circulation Research* 20:381, 1967.

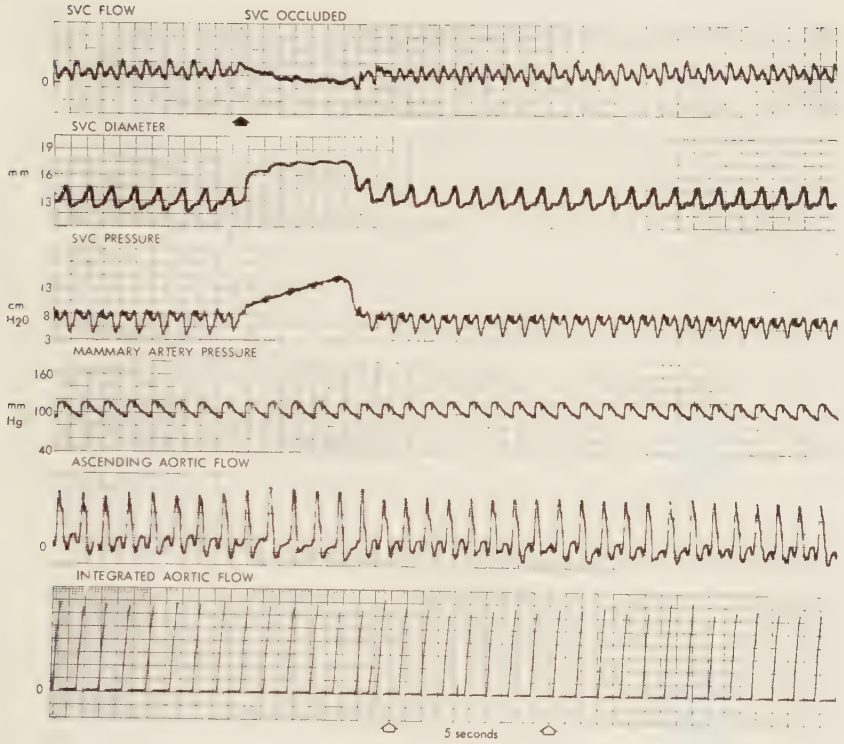

Fig. 2. The effect of brief occlusion of the superior vena cava, just above the atrial juncture, on caval diameter (ultrasonic transducer), distending pressure, and caval flow (PUFM). The animal was a chronic preparation; for brief occlusions, no "subjective" disturbances were noted in this dog. Reproduced, by permission, from *Circulation Research* 28:554, 1971.

For most chronic animal studies, the experimental hypothesis being tested rarely requires precise calibration of a flowmeter. Most studies involve the measurement of the effects of specific interventions such as exercise, shock, or drug administration. Comparison of flow before and after the intervention, particularly for a group of animals, is more intelligibly expressed as a percent of the basal flow. The only requirement for this type of normalized flow data is an accurate zero flow determination and a low-drift flow meter.

The pulsed ultrasonic flowmeter involves complex circuitry, and ease of operation is not one of its better features. I doubt that the marginal flow signals from small veins can be regularly recorded without the help of a resourceful and talented technical crew. The complex electronics also make unlikely the development of a telemetered signal. However, we have not found the "umbilical cord" between the animal and recorder a disadvantage in nine years of flow measurement.

The use of ultrasound for flow measurement was facilitated in our laboratory by the electronic and animal work with ultrasonic transit time dimension transducers. The instruments which we currently use can be operated in either modality, displacement or flow, a real saving in rack space. All of the units are synchronized, so that there are no problems with cross-talk.

Considering the costs of commercial models of most flow probes, the ease of construction of flow probes is a substantial consideration. The flow probes for our PUFM are constructed in our own laboratory, of dental acrylic poured in precisely machined molds in a wide variety of sizes. The positioning of the piezoelectric crystals is critical, but if the molds are correctly aligned, there is no real difficulty. The small crystals are cut from 1-inch square crystal stock. We now use lead zirconate-titanate crystals. The probes are bivalved, and secured with umbilical tape. The probe is coated with liquid silastic as a final treatment. Since there is no requirement for a uniform wall thickness such as is imposed by electromagnetic probes, the PUFM flow probes have a particular advantage in the simultaneous measurement of flow at the aortic and pulmonic roots (Fig. 1).

Although most of our work with flowmeters has been in chronic animal studies, a brief word should be added about the use of ultrasonic probes in acute experiments. Obtaining flow signals depends on adequate acoustical coupling. This can be achieved by using a probe that is slightly smaller than the vessel, but the vessel may be misleadingly small with the chest open. To avoid compromising the vessel lumen after recovery, a slightly larger probe can be used, and acute recordings can be obtained by flooding the field with saline (Fig. 3), or by the use of an acoustical gel in the probe.

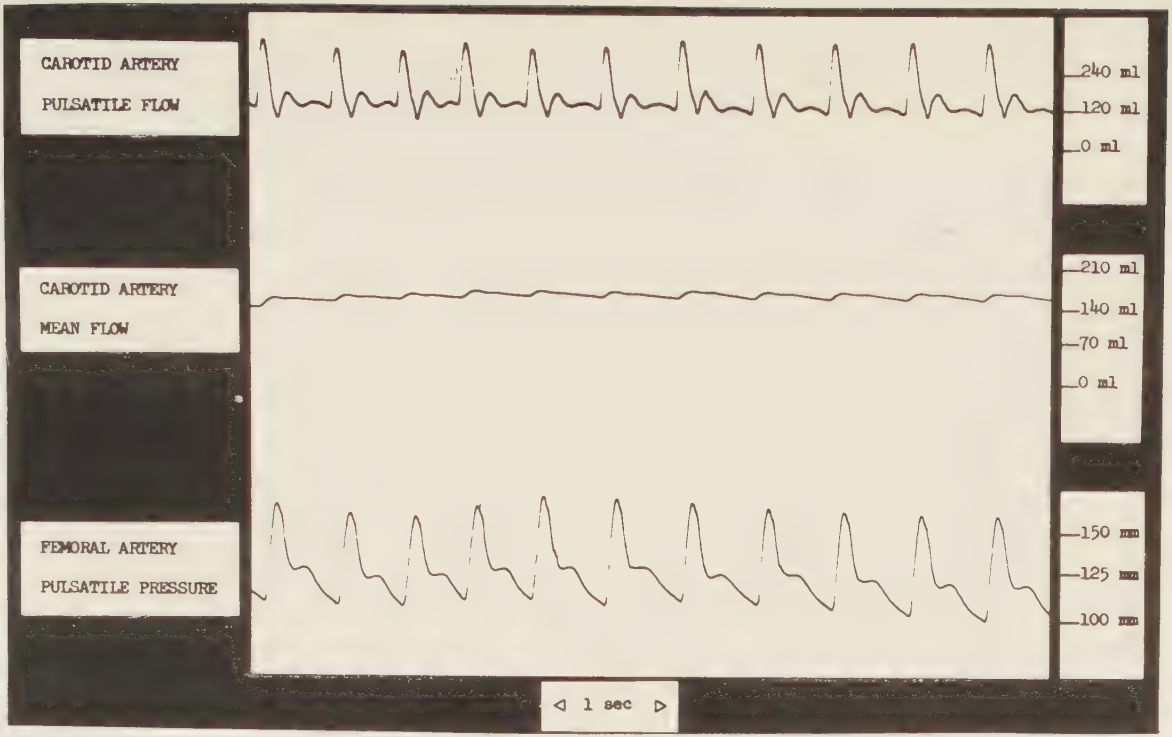

Fig. 3. A recording from an acute dog experiment. Flow measurement in the carotid artery was obtained with a flow probe equipped with flush lines for saline irrigation in the event of loss of acoustical coupling. Calibration was obtained terminally by collecting blood in a graduated cylinder, timed with a stop watch.

SUMMARY

Pulsed ultrasonic flow probes are light weight and provide reliable flow signals in chronic animal experiments. There are no problems with artifacts from the ECG signal, and reversed flow is faithfully recorded. Zero flow may be determined by acetylcholine arrest or by mechanical, implanted occluders. The electronic operation is somewhat complicated and skilled technical help is important. The flow probes are relatively easy and inexpensive to construct.

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9. THERMODILUTION IN CHRONIC EXPERIMENTATION

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SYSTEMIC THERMODILUTION (Cardiac Output Determination)

Instead of an introduction, I would like to start with a question: Why has the thermodilution technique received relatively little acceptance, in spite of a number of obvious advantages? I think that part of this hesitant approach is related to inadequate instrumentation—I shall try to summarize these circumstances under "Technical Notes"—but the reluctance is based mainly on unclear heat transfer conditions which, it was feared, might lead to heat loss between the sites of injection and sensing. The original report by Fegler (1), describing the successful determination of cardiac output by injecting cold saline and sensing the resulting temperature transient downstream, was very soon criticized by Dow (2). This prompted a number of more exactly controlled studies (3, 4) which can be summarized by the statement that under well-defined conditions these losses may be negligible. An analysis of these reports, prior to 1962, is included in Hosie's review (4). Taking into account also more recent reports (5, 6, 7, 8) (Fig. 1), we may conclude that reliable measurement results can be expected if the injection site is close to the right atrium or left ventricle and the sensing element is positioned in the pulmonary artery or any systemic artery, respectively. It has to be pointed out that, in contrast to the dye injection technique, thermodilution cannot be used reliably for mean pulmonary circulation time determination because specific heat transfer conditions in the pulmonary circulation affect the time course of the curve, without influencing its area.

LOCAL THERMODILUTION (Single Vessel Flow Determination)

In contrast to systemic thermodilution, local thermodilution (LTD) is defined as the technique in which the site of injection and sensing are close

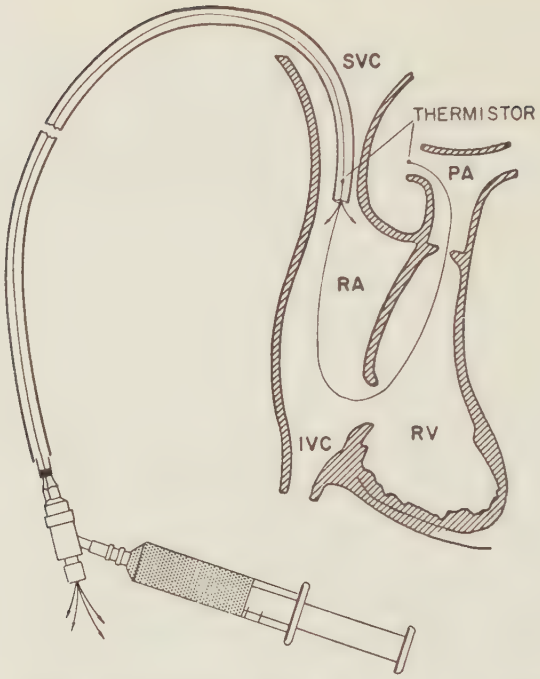

Fig. 1. Cardiac output thermodilution set-up (from [8]): SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PA = pulmonary artery.

to each other, from several millimeters to a few centimeters (9) (Fig. 2). The proximity of these two sites offers several advantages: the possibility of measuring blood flow in a single vessel, fast repetition rates of measurement, and no recirculation. On the other hand, these conditions introduce new problems which have to be considered. For instance, the very short distance imposes stricter constraints on the mixing, which has to be complete within several millimeters. In addition, this proximity produces another problem; the initial part of the dilution curve is being recorded at a time when the injection is not yet completed. It has been shown (9) that when arterial blood flow is measured, this factor does not affect the flow rate because the injectate simply replaces the blood temporarily. On the other hand, if venous blood flow is measured, the injection of the bolus may cause a transient increase in blood flow and a correction was suggested (9). In our experience, venous flow rates above 60 ml / min do not require this correction.

In the past decade, the principle of local thermodilution was successfully applied to blood flow in several vessels. For instance, blood flow was studied in man in the femoral and iliac arteries, and in the femoral vein (10, 11, 12). Specially modified local thermodilution catheters were constructed and published by a number of authors (13, 14). However, the complexity of these catheters does not permit successful long term implantation. On the other hand, Chalmers and co-workers (15), and White and co-workers (16), have successfully implanted miniaturized local thermodilution catheters to measure portal and renal venous blood flow.

One of the most interesting areas of local thermodilution application is the measurement of coronary sinus outflow. This technique has also been used in man (17), but long term implantation does not seem to be possible because of anatomic conditions specific to the coronary sinus. However, it is conceivable that this technique can be used under semi-chronic conditions by inserting the catheter under local anesthesia. With suitable precautions and heparinization, the catheter may remain in the coronary sinus for 24 hours.

Generally, the thermodilution catheters need not be removed after each measurement or after each session. An additional application which is not well known is the implantation of several catheters in side branches, for instance, of the aorta or through the wall of the aorta at strategic sites (Fig. 3). In this case, the thermistor or the sensing element is located distally (in the iliac or femoral artery), and can be mounted on a very thin catheter inserted via the femoral artery using the Seldinger technique as will be described below. This approach (13) makes it possible to measure different blood flows because, as is well-known with any dilution technique, the area

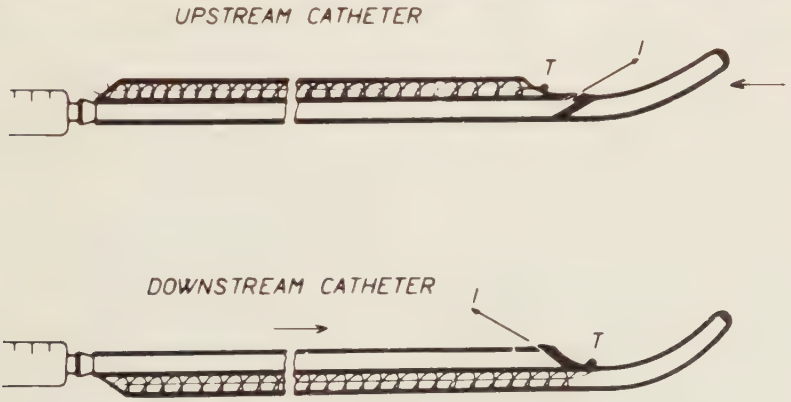

Fig. 2. Local thermodilution catheters. T = thermistor; I = injection orifice.

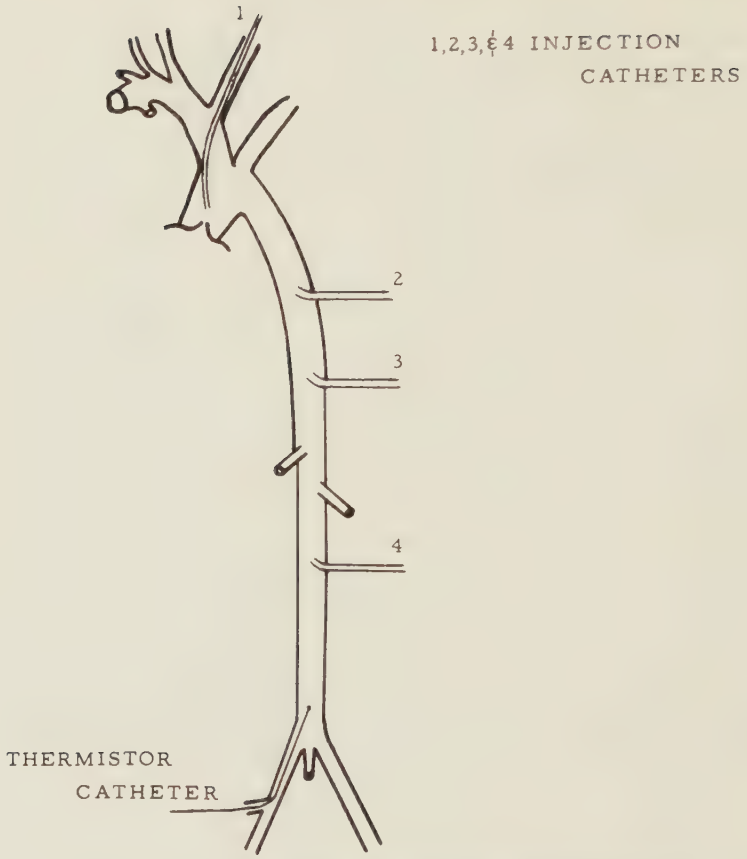

Fig. 3. Multiple injection sites using one thermistor catheter.

under the dilution curve is related inversely to the blood flow at the site of injection, provided there is no additional inflow of "uncontaminated" blood.

Finally, a local thermodilution catheter can be inserted under local anesthesia utilizing the Seldinger technique. It requires the puncture of an artery (under local anesthesia), usually the femoral artery, insertion of a guide through the needle, and then threading a tapered catheter over the guide. The guide is then removed and the catheter carrying the thermistor and injection orifice can be guided to the required measurement site.

As shown in Figure 4, systemic and local thermodilution can be advantageously combined. A local thermodilution catheter is monitoring the coronary sinus outflow, and an additional thermistor catheter inserted

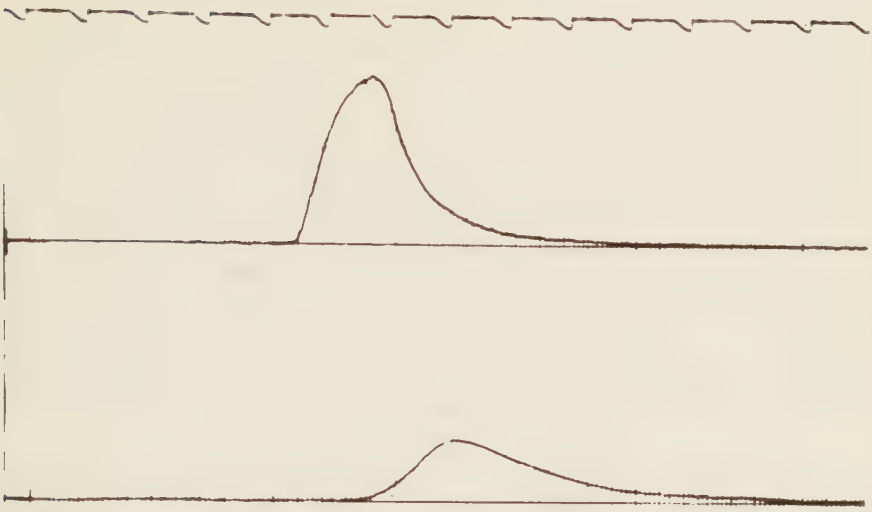

Fig. 4. Simultaneous determination of coronary sinus blood flow and cardiac output. Upper tracing coronary sinus blood flow, lower tracing cardiac output. Time in seconds.

into the pulmonary artery monitors the temperature transient caused by the cold bolus arriving from the coronary sinus, mixing with the total blood flow, and thus recording cardiac output.

TYPE OF INJECTION (Single vs. Continuous Injection)

As with the dye dilution technique, two types of injection can be used: continuous or a single slug injection. The advantage of the former is that, since a temperature steady-state is recorded, the evaluation is simple, and under standardized conditions, the deflection is the only variable. Dynamic changes in blood flow may therefore be recorded and especially if small changes in blood flow are expected, a continuous sensing may be more reliable than a single dilution curve with all its curve-to-curve variability. However, the disadvantages seem to be rather significant. In order to obtain a proper signal-to-noise ratio, an average infusion rate of 50 ml / min is used for at least 20-30 sec., and if 5 to 15 measurements are to be performed, the amount of saline introduced into the cardiovascular system is not negligible. Pavek and co-workers (18) have shown, for instance, that to obtain reliable mixing (in cardiac output determinations), a continuous injection rate of 1-2 ml / sec seems to represent the minimum. Smaller blood flows (mammary artery-goat) have been measured with a continuous

infusion technique by Linzell (19). With an injection rate of 20-50 ml / min, good results have been obtained at flow rates up to 1000 ml / min. It has to be emphasized that proper mixing is closely related to the kinetic energy of the indicator jet leaving the orifice (9, 20), and therefore, the injection rate has to be considered in conjunction with the size of the injection orifice. In comparison to the continuous infusion technique, the single slug injection has the advantage of a higher signal-to-noise ratio, and negligible loading of the animal with saline. Evaluation of results, though more tedious than with the continuous infusion technique, can be highly simplified by using electronic integration. With local thermodilution this process is quite simple.

PROCESSING OF THERMODILUTION CURVES

One of the advantages of the thermodilution technique is that recirculation is very small even under systemic application (cardiac output determination). It is completely negligible with local thermodilution where the site of injection and site of sensing are very close, from several millimeters to several centimeters. This eliminates the requirement of integration combined with logarithmic extrapolation as required for the processing of dye-dilution curves. Recently a number of single purpose computers became commercially available and most of them compare favorably with standard computation procedures (21, 22, 23, 24). In view of the fact that logarithmic extrapolation is not required, a very simple system can be utilized which basically only divides the integral into an arbitrary constant. The result can be either displayed directly or multiplied by two constants (amount of injectate and the blood-injectate temperature difference).

TECHNICAL NOTES

Although the basic instrumentation for temperature determination in a moving medium is relatively simple, it is surprising that it has been sometimes over-simplified by overlooking the self-heating effect of the thermistor. Most authors have been aware of the fact that there is a certain amount of dissipation which must not be reached if velocity sensitivity of the thermistor is to be avoided. James and co-workers (25) have shown that for the given conditions, the power input must be below 0.01 milliwatts. Vliers and co-workers (26) have recently concluded that higher resistance thermistors (100 KΩ at 25°C) are preferable to the usual low resistance units (2 KΩ at 25°C) because the higher thermistor resistance yields lower dissipated power. In this context, I would like to add one additional feature

which is not fully utilized in the flow and velocity measurements. It is well known that "overheating" of the thermistor can be used very conveniently to measure velocity (27, 28, 29). This technique, however, has not met with wide acceptance, most probably due to several technical drawbacks: non-linearity, low frequency response, and mainly, lack of directional sensitivity. Recently Grahn and co-workers (30) have described a comprehensive electronic design linearizing the resistance / velocity relationship, increasing the frequency response and most significantly, incorporating directional sensitivity. The local thermodilution principle for measuring blood flow combined with the "overheated" or velocity sensitive thermistor (for instance, by increasing the voltage after completion of the injection) could combine the advantages of a single flow determination with continuous velocity monitoring. A prerequisite, of course, would be that the vessel diameter changes be negligible during the velocity recording.

ADVANTAGES AND DISADVANTAGES OF THE THERMODILUTION TECHNIQUE

Summarizing the different aspects of the thermodilution and local thermodilution technique, it can be said that the advantages are as follows: very little recirculation or in the case of local thermodilution, no recirculation at all. This leads to a very simple integration procedure. Rapid repetition of the single injections is also possible. The next factor, quite important in chronic animal experimentation, is that there is no need of blood withdrawal. This factor is still under-estimated in clinical physiology or intensive care units, but it is sometimes not fully appreciated even under experimental conditions where additional blood removal may influence drastically the experimental results, as for instance, in shock, etc. Finally, since saline or autologous blood can be injected, no toxic effects can be expected with practically unlimited numbers of injections in contrast to the dye-dilution technique. On the other hand, the heat transfer conditions in the lungs impose a severe limitation to the determination of pulmonary mean circulation time.

SUMMARY

The thermodilution technique and the local thermodilution principle can be successfully used in chronic experimentation by utilizing all the experience which has been gained by many authors with implantation of catheters, either with long-term implantation or catheterization under conscious conditions and local anesthesia, thus making it possible to measure blood flow under non-anesthetized conditions.

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10. DETERMINATION OF RENAL BLOOD FLOW BY EXTERNAL COUNTING OF XENON^{133} DISAPPEARANCE RATE[1]

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Evidence has accumulated, in recent years, which purports to show that changes in renal blood flow and shifts in the distribution of flow within the kidney may contribute to important changes in renal function (1, 2). Intrarenal hemodynamic factors have been implicated in the modification of sodium metabolism associated with circulatory stress, such as essential hypertension and congestive heart failure (3, 4). On the other hand, Rushmer and colleagues (5) showed in 1961 that there is minimal change in renal blood flow to a balanced stimulus, such as exercise, unless the dog is alarmed. They did find reductions in renal flow to hypothalamic stimulation and to infusions of catecholamines or pitressin in the conscious dog with ultrasonic flowmeters implanted on the renal artery. Van Citters and Franklin (6) confirmed the finding with respect to exercise by showing that even in prolonged and maximal effort during cross-country runs by Alaskan sled dogs, blood flow to the kidney was not reduced. However, Wilson and Iriuchijima (7) found renal blood flow to be very sensitive to mild neurobehavioral stimuli in the laboratory using chronically implanted flow sensors, and with the dogs in a psychologically neutral setting. Changes in renal flow were shown to be mediated by sympathetic adrenergic fibers. With treadmill exercise the change in mean renal flow was minimal, though transient fluctuations could be elicited as an alerting response to a variety of signals.

Increased sodium excretion occurs with the chronic administration of vasopressin, apparently due to the retention of water and the resultant extracellular volume expansion (8, 9). Likewise, continuous endogenous release of ADH occurs due to various stimuli, such as the thirsting state or surgical stress, and is responsible for maintaining plasma ADH concentra-

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tions. While examining the dose-response relationship between plasma ADH concentrations and renal blood flow, measured with the electromagnetic flowmeter in anesthetized and awake chronic dog preparations, Pullella, Moran and Wilson (10) observed increased renal blood flows at intermediate plasma ADH concentrations, up to 16μU/ml, with no change in mean arterial pressure. This apparent reduction in renal vascular resistance to a constant infusion rate of arginine vasopressin (ADH) demanded closer scrutiny. Since shifts in the distribution of flow within the kidney may influence sodium excretion, correlation between the measurement of intrarenal blood flow distribution and renal function studies is important. A flow sensor implanted on the renal artery cannot discriminate between flows to different regions of the kidney. In order not to interfere unduly with the physiological state of the animal, we selected the technique of externally counting the disappearance rate of the radioactive inert gas $Xenon^{133}$ to measure the desired distribution of intrarenal blood flow (11).

SELECTION AND PREPARATION OF DOGS

The experimental dogs must be selected carefully in terms of their temperament and also with respect to anatomical characteristics of the arterial blood flow within the kidney. We found that a spirited but well-mannered dog would accept a stomach tube, with minimal restraint while sitting quietly, for purposes of giving a 5% body weight tap water gavage to inhibit endogenous ADH. By percutaneous insertion through the femoral artery, a catheter was placed in the renal artery using fluoroscopy, and radiocontrast medium was injected. If the vascularity of the kidney exhibited filling defects or there was more than one renal artery leaving the aorta, the dog was rejected. The indwelling arterial 4 Fr Teflon catheter was then used for rapid injections of $Xenon^{133}$ directly into the renal circulation. Since nearly 100% of the $Xenon^{133}$ decay occurs with a gamma emission, in contrast to only 0.6% of the $Krypton^{85}$ decay, very small quantities can be used. Our technique is to place 0.15 ml of $Xenon^{133}$ solution, containing 1 millicurie, into the indwelling renal catheter whose volume is 0.25 ml, and then to flush the solution very quickly into the kidney with 0.5 ml of heparinized saline.

Blood pressure was measured via the femoral artery. For renal function studies additional catheterizations were required for collection of urine, drawing blood samples, and for infusions. These were performed in a reasonably atraumatic manner as judged by measurements of the concentration of ADH in the plasma, which were consistently lower than 1 μU/ml. Such concentrations indicate essentially no endogenous production of

ADH, a sensitive indicator to pain and excitement (12).

EQUIPMENT AND DISAPPEARANCE CURVES

Disappearance of $Xenon^{133}$ from the kidney was detected with a Nuclear Chicago Pho-Gamma III (scintillation) camera having a 12 inch sodium iodide crystal behind a pinhole collimator with the pinhole removed, giving a 2 inch opening directly over the kidney. This provided an initial washout to background radiation level (i.e., signal to noise ratio) of 100 to 1. The scintillations from the crystal activate an array of photomultiplier elements. Then, the data are processed by an Intertechnique hard-wire programmed digital computer system, and plotted on semi-log graph paper with an X-Y plotter. The composite washout is interpreted to be the sum of 2 exponential washouts associated with blood flow in 2 regions of the kidney: the outer cortex, and the juxtamedullary cortex plus outer medulla. Exponentials associated with the 2 blood flows are sufficiently fast and different to allow quantification by graphical analysis of the semilogarithmic plot. The technique accounts for about 95% of the blood flow to the kidney, excluding only flow to the inner medulla and the renal fat pads. The washout yields counts per second as a function of time: $A(t) = A_1 e^{-K_1 t} + A_2 e^{-K_2 t}$.

The graphical analysis technique results in the 2 exponentials being displayed as separate straight lines. The slopes, K_j, of the equation are equal to the blood flow per unit volume of the respective regions.

BASIC THEORY AND EQUATIONS FOR ANALYSIS

The formulation that follows is adapted from that of Meier and Zierler (13, 14) whose particular theoretical treatment avoids some of the vulnerable assumptions related to homogeneity of tissue or compartments and does not assume an equilibrium of blood and tissue concentrations.

If the rapid intra-arterial injection of tracer approximates an impulse at the entrance to a system, the resultant concentration versus time curve at the exit of the system is characterized by: (1) delayed appearance of tracer, (2) splayed peak concentration, and (3) return of tracer concentration to zero in the absence of recirculation (Fig. 1). The characteristic shape of the concentration versus time curve is caused by tracer molecules having different transit times. As shown in Figure 1, the frequency function, h(t), of these transit times equals the product of the concentration function, c(t), and the ratio of blood flow to the amount of tracer injected, $\dot{V}/A_O$. For steady state blood flow conditions during the period of measurement, the

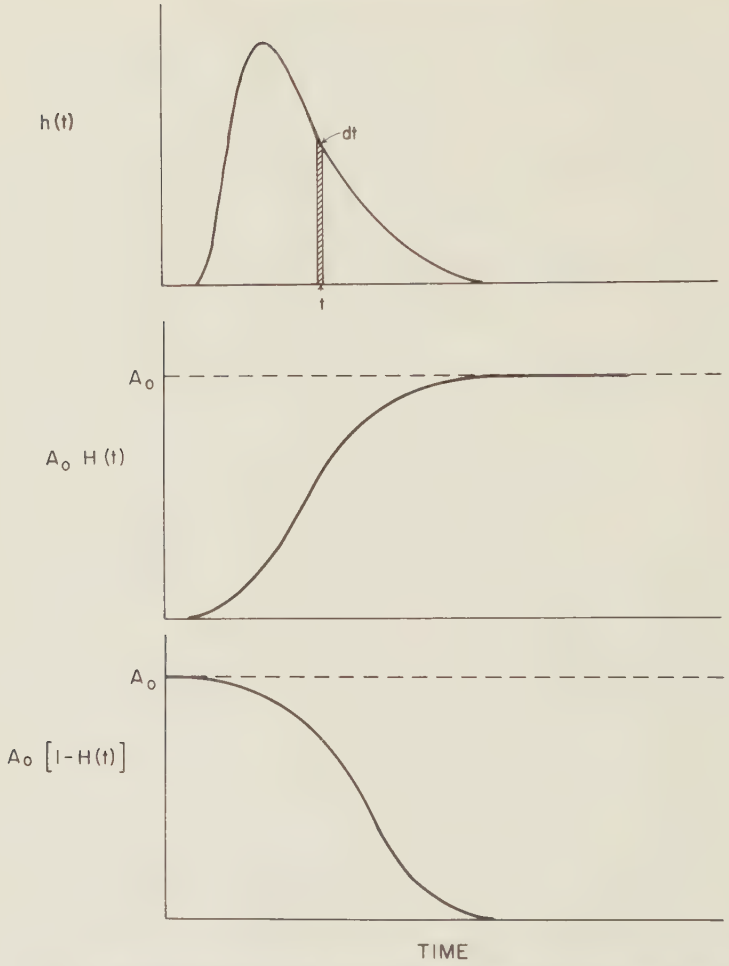


Fig. 1. Upper graph. Concentration versus time at the exit of a system when tracer was given as an impulse and no recirculation occurs. The characteristic shape of the concentration function, c(t), is caused by tracer molecules having different transit times. The frequency function, h(t), which equals the product of a constant and c(t), therefore having the same shape as c(t), is the fraction of tracer leaving the system per unit of time.

Middle graph. The amount of tracer that has left the system as a function of time equals the amount given times the cumulative frequency function, A_o H(t).

Lower graph. The amount of tracer remaining in the system, A_o [1–H(t)], as measured by external counting.

shape of the concentration function does not change. Since a given amount, A_o, is injected, the frequency function equals the product of a constant and the concentration function, and also does not change. That is,

$$A_o h(t)dt = \dot{V}c(t)dt \tag{1}$$

$$\text{and} \qquad h(t) = \frac{\dot{V}}{A_o} c(t). \tag{2}$$

It should be emphasized that the frequency function equals the fraction of tracer leaving the system per unit time. This can most easily be seen by simple dimensional analysis,

$$h(t) = \frac{V/t}{M_i} \times \frac{M_o}{V} = \frac{M_o}{M_i} \times \frac{1}{t}. \tag{3}$$

The ratio of the mass out, M_o, to the mass injected, M_i, per time is the fraction of tracer leaving per unit of time and has a particular transit time. Thus, the frequency function is the frequency of occurrence of transit times.

The cumulative frequency function is:

$$H(t) = \int_o^t h(t)dt. \tag{4}$$

Thus, the frequency function integrated over all time equals one, the concentration function approaches zero when there is no recirculation, and all tracer will have left the system. The amount of tracer that has left the system by some intermediate time is equal to the amount injected, A_o, times the cumulative frequency function integrated from zero to that time (as shown in middle trace of Figure 1). The amount of tracer remaining in the system is, therefore, the product of the amount injected and one minus the cumulative frequency function (see lower trace of Figure 1). That is,

$$A(t) = A_o[1-H(t)]. \tag{5}$$

It can be shown that the fraction remaining, [1-H(t)], integrated over all time equals mean transit time, $\bar{t}$. That is,

$$\bar{t} = \int_0^\infty [1-H(t)]dt. \tag{6}$$

It follows that the amount of tracer remaining, A(t), integrated from zero to infinity equals the amount injected times mean transit time, or

$$A_o \bar{t} = \int_o^\infty A(t)dt. \tag{7}$$

Thus, $$\bar{t} = \frac{\int_o^\infty A(t)dt}{A_o}. \tag{8}$$

Mean transit time is also the volume to flow ratio in any system, $\bar{t} = V/\dot{V}$. Therefore,

$$\frac{V}{\dot{V}} = \frac{\int_o^\infty A(t)dt}{A_o}. \tag{9}$$

When a tracer is introduced as an impulse, its concentration is not uniform over the entire volume of distribution. However, the volume of distribution from an impulse injection equals that from a constant infusion producing a steady state concentration. In either situation the actual volume of distribution of tracer equals a constant which is characteristic of tracer times the total tissue volume, $V = \gamma V_i$. For lipid soluble inert gases, such as xenon, krypton and hydrogen, the constant, γ, is approximately one. Thus, the volume of distribution of tracer, V, shown in Figure 2, would fill the rectangle to equal the actual tissue volume, V_i. By substitution the ratio of volume of distribution to flow, $V/\dot{V}$, can be expressed by the ratio of a fraction of total tissue volume to flow, $\gamma V_i/\dot{V}$. The equation is,

$$\frac{V}{\dot{V}} = \frac{\int_o^\infty A(t)dt}{A_o} = \frac{\gamma V_i}{\dot{V}} \tag{10}$$

and the concept of a partition coefficient has not been used, which is to say it was not necessary to make any assumptions about an equilibrium between blood and tissue concentrations of tracer.

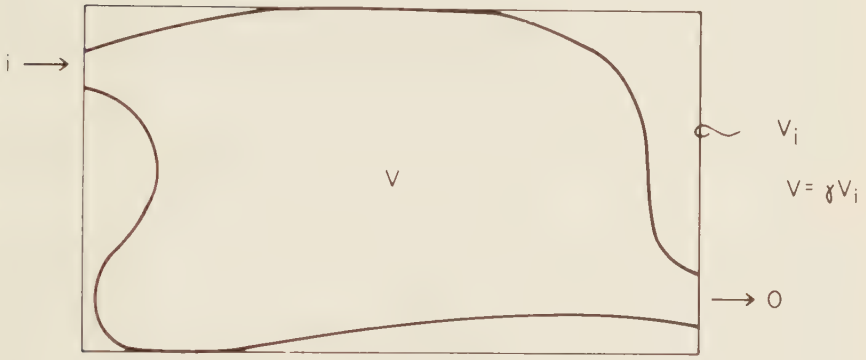
MULTICOMPONENT SYSTEM ANALYSIS

The data, as measured with an external scintillation detector, are displayed as the amount of tracer remaining as a function of time (Fig. 3). The amount of tracer remaining in the system was previously shown to be,

$$A(t) = A_o[1-H(t)]. \tag{5}$$

The tail of this function has been assumed to be the sum of two or more exponentials. That is,

VOLUME OF DISTRIBUTION OF TRACER



$$\frac{V}{\dot{V}} = \frac{\int_0^\infty A(t)\,dt}{A_0} = \frac{\gamma V_i}{\dot{V}}$$

Fig. 2. The rectangle, V_i, is the total volume of the system and V is the volume of distribution of tracer within the system.

$$A(t) = \sum_{j=1}^{n} A_{oj} e^{-k_j t}, \tag{11}$$

where $k_j = 1/\bar{t}$, and is the slope of the j^{th} exponential found by the method of peeling of a semilogarithmic plot of the data. Since mean transit time is the ratio of tissue volume to flow,

$$\bar{t} = \frac{\gamma V_i}{\dot{V}} \tag{12}$$

then the flow per unit tissue volume in the j^{th} compartment equals the slope of the j^{th} exponential, which, in turn, is proportional to the amount injected into that compartment over its unit tissue volume, that is,

$$k_j = \frac{\dot{V}_j}{\gamma V_{ij}} \propto \frac{A_{oj}}{\gamma V_{ij}}. \tag{13}$$

Dividing by the density of the particular tissue produces the expression, blood flow per gram of compartment tissue. Compartmental flow is commonly expressed in ml/min/100 g of tissue.

To find total blood flow, in all compartments, the fractional volume of each compartment must be known. Since $\gamma V_{ij} \propto A_{oj}/k_j$, (that is, the volume of the j^{th} compartment is proportional to the ratio of the amount injected to the slope associated with that compartment), then,

$$ {}^{f}V_j = \frac{\gamma V_{ij}}{\sum_{j=1}^{n} \gamma V_{ij}} \tag{14} $$

which states that the fraction of volume in compartment j equals the ratio of the volume in compartment j to the sum of volumes in all compartments.

Total blood flow per gram of tissue in all compartments over which the tracer was distributed is then computed by summing the products of the fractional volume of each compartment and the compartmental flows per unit tissue volume. Then, the expression for renal blood flow (RBF) per gram or 100 grams of kidney becomes,

$$ RBF = \sum_{j=1}^{n} {}^{f}V_j \frac{\dot{V}_j}{\gamma V_{ij}} \tag{15} $$

In renal blood flow measurements, one should not attempt to differentiate beyond two compartments. For $n > 2$: (a) blood flows are very slow due to trapping and deviate from k substantially, and (b) the slope, k, is small, making analysis inaccurate.

Our data analysis by the method of peeling of a semilogarithmic plot of the data considers all scintillations beyond the 200th second to be due to background radioactivity. The radioactivity at the 200th second is then subtracted from a curve which is spline-fitted, by hand, to the multi-exponential data. Then a tangent is fitted to the tail of the resultant curve, yielding the slope, K_2 for compartment II; which is again subtracted from the remaining exponential data plot, leaving a single exponential recorded as the slope, K_1, for compartment I. The semilogarithmic data plot is now done electronically with a logarithmic data card placed in the data analysis system ahead of the X-Y plotter. This procedure has eliminated the problem of hand-fitting of the data points.

Our results from a series of intrarenal blood flow measurements by the external counting of $Xenon^{133}$ disappearance rate show total renal blood

COMP.	T1/2 (min)	K=0.693/T1/2 (min-1)	COMP. FLOW (ml/min/100g)	Ao (CPS)	Ao/K	f	TOTAL FLOW (ml/min/100g)	% OF TOTAL FLOW
I	0.200	3.46	346	6,100	1,760	0.47	163	73%
II	0.616	1.12	112	2,200	1,960	0.53	59	27%
				8,300	3,720	1.00	222	100%

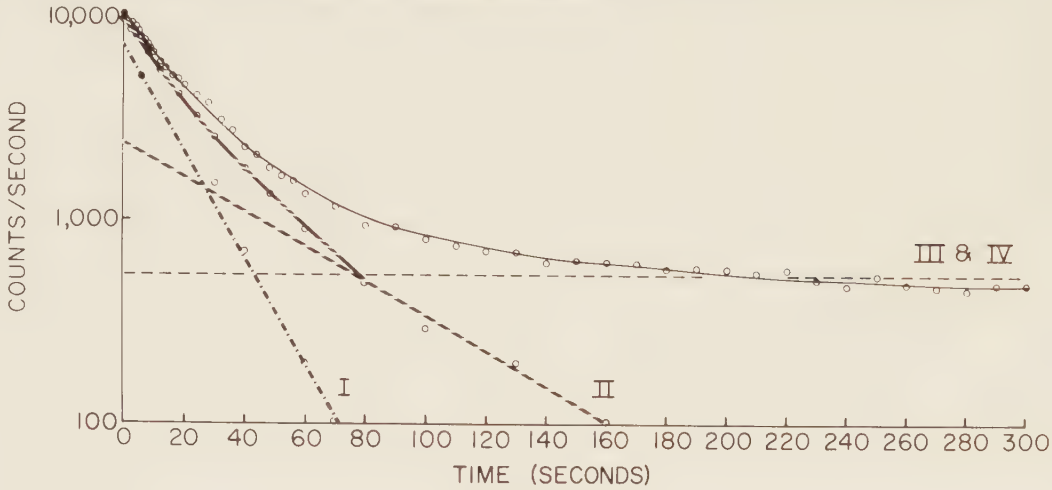


Fig. 3. External counting of Xenon^{133} disappearance as a function of time from the right kidney, weighing 64 grams, of a dog during ADH infusion which yielded a predicted plasma level of 1 μU/ml.

flow per 100 grams of kidney, and the magnitude of change due to experimental intervention, to be more accurate than our measurements using the chronically implanted electromagnetic flow probe. The $Xenon^{133}$ external counting technique also permits evaluation of shifts in the intrarenal distribution of blood flow for correlation with concomitant renal function studies.

SUMMARY

Since changes in renal blood flow and shifts in the distribution of blood flow within the kidney may contribute to important changes in renal function, and under certain conditions renal blood flow is quite labile, it is necessary to measure flow and the distribution of flow in a manner which will not interfere unduly with the physiological state of the animal. The technique of external counting of the disappearance rate of the radioactive gas $Xenon^{133}$ satisfies this condition.

The basic theory and equations for analysis have been presented in a manner which avoids some of the vulnerable assumptions related to homogeneity of tissue or compartments. An application of this theory to a multicomponent system of blood flow such as the kidney is discussed, and the limitations are pointed out.

The method of data collection and data reduction are described with emphasis on the technique of graphical analysis.

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11. DYE DILUTION TECHNIQUES FOR CALIBRATION OF CHRONICALLY IMPLANTED FLOWMETERS[1]

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Although the electromagnetic and ultrasonic flowmeters are well suited for moment-to-moment measurement of flow in acute as well as chronic studies, the output of the meters cannot be accurately related to flow without calibration. Both types of meters measure velocity, not flow. Accurate calibration before implantation might seem possible when the outside of the vessel is fixed to a given diameter by a pre-calibrated probe, but vessel wall characteristics and asymmetry of the flow profile influence the calibration. Changes in hematocrit also affect calibration, especially if the input impedance of the amplifier is low, e.g., Biotronex units with 10 K ohm input impedance. For these reasons, an independent method of calibration is usually desirable.

The graduate and stopwatch technique is the ultimate of simplicity, but for cardiac output, the procedure is not easy and obviously can be done only at the end of the experiment, at which time the flow probe adhering to the aorta is removed from the animal and the system perfused with blood. Thus, some other technique is often needed to provide the calibration factor at intervals throughout a long-term experiment. Indicator dilution techniques using dyes, such as indocyanine green, provide an acceptable method if the basic assumptions are met.

The equation for the calculation of cardiac output is:

$$\text{Cardiac Output} = \frac{\text{Amount injected}}{\text{Minute-Concentration}} = \frac{A}{\int_0^\infty C\,dt} \qquad (1)$$

If a known amount of proper indicator is injected and a valid measurement of minute-concentration ($\int_0^\infty C\,dt = \overline{Ct}$) obtained, then a reliable estimate of cardiac output can be made. Zierler (1) has provided a review of the background and theory. The following provides an intuitive outline (Fig. 1):

[1] These studies were supported, in part, by Public Health Service grants HE07723 and H6308.

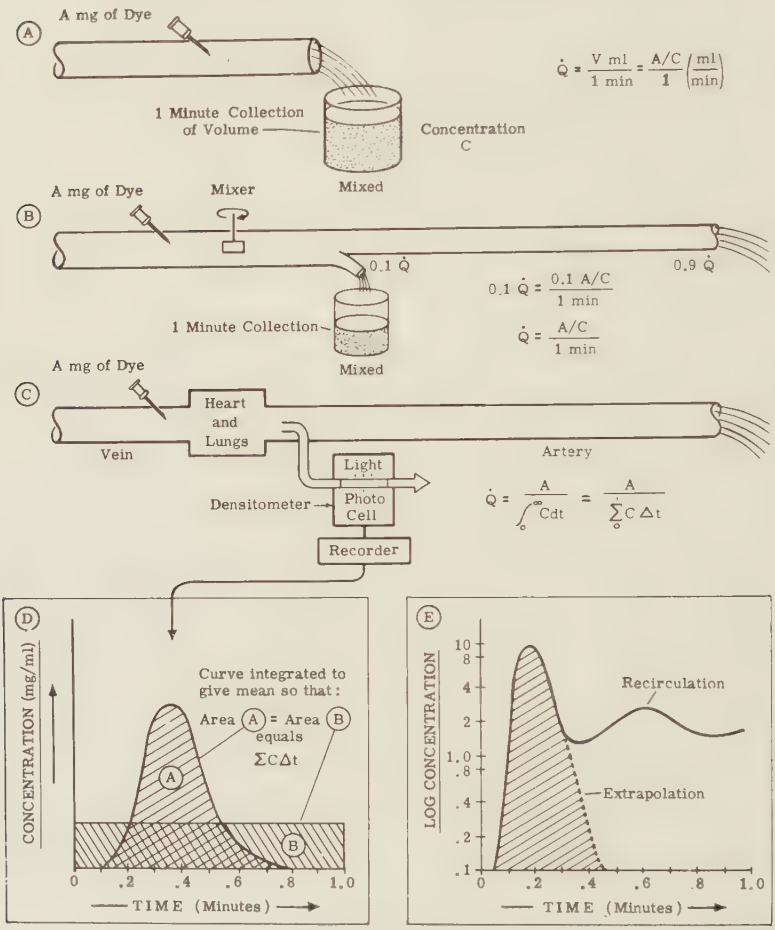

Fig. 1. Derivation of the Stewart-Hamilton indicator dilution equation for the measurement of cardiac output by the dye dilution method. A. Total flow stream collection. B. Collection of a fraction of the flow stream with no recirculation. C. Measuring dynamic concentration changes with a densitometer. D. Record of dye concentration and the derivation of the concentration-time factor, which is usually the mean concentration during 1 minute, i.e., the minute-concentration. E. Effect of recirculation and the method of extrapolation using a semi-logarithmic plot of dye concentration. Reproduced, by permission, from Rothe CF, Chap. 11, "Fluid Dynamics." In Selkurt EE, Ed. *Physiology* (3rd edition), Boston: Little, Brown. 1971.

First, imagine a flowing stream (Fig. 1A). If the total flow is collected over one minute, and the dye is mixed carefully, the volume per minute can be calculated from: $V = A/C$, which is a rearrangement of the equation defining concentration: $C = A/V$.

Next, (a) if the dye is mixed across the flow stream, (b) if a definite proportion (assume one-tenth) of the flow is collected (Fig. 1B), starting before the dye appears and ending after the dye has cleared the sampling site, (c) if the volume containing dye is collected for one minute and is thoroughly mixed so that the mean concentration may again be determined, and (d) if the proportion of the total amount of dye injected is exactly equal to the proportion of the total flow collected over one minute (i.e., one-tenth of each), then the total flow can be calculated. Since the proportionality constants for the dye and the volume are equal, it is not necessary to know what proportion of the flow is collected. This proportion must, however, be constant throughout the collection, and the dye must be uniformly mixed across the flow stream.

Finally, instead of collecting a sample over a given time interval and mixing, individual samples may be analyzed or a continuous measure of the indicator concentration may be made with a densitometer (Fig. 1C). The mean concentration, $\overline{Ct}$, is calculated (Fig. 1D) over the time interval, usually one minute. This minute-concentration is a term somewhat analogous to the respiratory minute-volume. Usually, after less than a minute, the concentration has declined to a level so near zero that no further additions are made to the sum, if no dye recirculates past the injection site.

Following Zierler's line of thought for an intuitive argument (1) and one that is more mathematical than the above, the rate of appearance of indicator at the outflow of the system at each instant is the product of the changing concentration, $C(t)$, and the flow, $\dot{Q}$, which is the rate of change of volume, V. Assuming that the entire amount of indicator, A, leaves the system, then summing all the instantaneous products of concentration and flow must give the amount of injected indicator:

$$A = \int_0^\infty \dot{Q}\, C(t)\, dt \qquad (2)$$

If some fraction, k, of the flow stream is sampled, $\dot{Q}/k$, and if we assume that the same fraction of the injected indicator is sampled, A/k, then:

$$A/k = \int_0^\infty (\dot{Q}/k)\, C(t)\, dt \qquad (3)$$

If we further assume that the flow, Q, is constant, it can be brought outside the integral. If we can assume that the indicator transverses the flow stream

at the same rate as the fluid, the coefficient, k, can be brought outside the integral, also, and can be cancelled, giving:

$$A = \dot{Q} \int_0^\infty C(t)\, dt \qquad (4)$$

On rearrangement, the basic indicator dilution equation is obtained. Note the assumptions made! To the extent that they are not valid, the equation is in error.

Because of its utility as well as the problems and pitfalls, the literature on indicator dilution techniques is voluminous. Only a few of the more recent developments will be presented, in terms of some of the assumptions and associated problems.

1. The indicator must be adequately mixed across the flow stream. The computed flow is, if course, based on the volume of dilution and so a flow which in effect bypasses the mixing site is not measured. The problem of mixing precludes accurate measurement of flow in a single blood vessel by injecting into the vessel at one point and sampling downstream. Many have tried the technique, but without special mixers, confidence in the accuracy of the results should not be high. On the other hand Bassingthwaighte et al (2), among others, have provided evidence that adequate mixing occurs in either the right or left ventricle. Injecting into the right ventricle and sampling from the pulmonary artery, however. leads to higher variability than is present when the sampling site is further downstream or the injection site is further upstream, and so is less reliable than having both ventricles aid in the mixing process.

2. There must be no loss (or gain) of indicator. This is particularly serious with indicators which can cross capillary walls. Thus, saline and thermal dilution are subject to these sorts of errors. Another problem has arisen because the commonly used indicator, indocyanine green (Cardio-Green; Hynson, Westcott and Dunning), is relatively unstable in aqueous solutions, especially in the presence of light or electrolytes. Because albumin stabilizes the dye, some investigators have routinely added plasma or albumin to the concentrated dye. This practice, not suggested by the manufacturer, leads to a 20 to 60% over-estimation (3) of flow in cases of rapid circulation time, since the apparent concentration is temporarily low—in effect, an apparent loss of dye. The optical properties of the dye change markedly on combining with protein and also on dilution of dye-protein mixture (3). Whereas the change on combining with protein is rapid (less than 2 seconds) (2), changing the concentrated dye-protein complex to the diluted form during the determination is slow (6-8 sec) (3). Adequate dye stability for a 6 to 12 hr period can be obtained by using the diluent

provided by the manufacturer to reduce electrolyte contamination, and by reducing the amount of light shining on the stock solution. Thus, plasma or albumin should not be added to the concentrated stock solution of dye.

3. Correction must be made for recirculation of dye. Since the indicator dilution curve is generally not completed before some dye passes through shunt paths and reappears at the sampling site, the effect of this recirculated dye must be discounted. Numerous techniques are available.

One approach is based on the assumption of an exponential decline in concentration after the peak value. The classical Stewart-Hamilton approach is to plot the data on semi-logarithmic coordinates, extrapolate to a low value and calculate the integral under the curve by adding ordinate values and dividing by the number of data points per minute. Alternatively, a planimeter may be used after transferring the extrapolated data points to the original curve. Logarithmic modules can be used to obtain the log of the data on an adjacent channel for extrapolation. Numerous investigators have developed digital computer algorithms for the task. Several analog devices are commercially available. In some, the area under the curve extrapolated from a given point to infinity is assumed to be a given factor times the area between two earlier points based on the mathematics of the integral of a decaying exponential. For example, the time-concentration area between the concentration at 60% of the peak value and that at 40% is exactly 1/2 of the area from 40% to 0%, the concentration at infinite time. This is because the value of the integral, i.e., the area from a given instant in time to infinity, is simply the product of the concentration at that point and the time constant. Another principle used is to compute the decay constant of the exponential decline and use this to compute the extrapolated area to infinity. One implementation of this technique will be described more fully in the data-processing section (Paper No. 47).

If the cardiac output is low, recirculation may start even before the peak indicator concentration is reached; then correction of recirculation of an exponential decay is impossible. One solution to this is to move the injection and sampling sites closer together (4). Although it is generally poor practice to inject the dye into a peripheral vein, under conditions of low cardiac output it is intolerable. Injection into the vena cava or right atrium via a fine bore catheter is much to be preferred. Injection into the left atrium may be convenient for cardiac output determinations in chronic animals and minimizes transit time. The ventricles are not perfect mixers, however (5). Rapid injection without flushing should be considered (6). Although sampling can be from the brachial or femoral arteries, sampling via a catheter at the arch of the aorta is best. High sampling rates (20-30 ml/min) are needed to minimize error from small changes in flow rate

causing changes in erythrocyte orientation and so optical density of the background. A short, small-bore catheter connected directly to the densitometer helps reduce distortion (smearing) of the curve, and so error. A catheter tip densitometer would be still better if the optical path length were fixed and monochromatic light were assured.

Another possible solution to the recirculation problem is to compute the area by assuming a gamma-function (7-9). The total curve is predicted using only the upslope and part of the downslope of the curve. Digital computation appears to be the only practical way of implementing this approach. High (0.99) correlation with the classical Stewart-Hamilton method was found, although the gamma-function method has yielded consistently high results (9). Yoder and Swan (9) also found that "for practical purposes, the gamma-function method does not eliminate more 'recirculation area' as cardiac index decreases." So far it has not been shown to be clearly superior to the more classical methods which assume one simple exponential decrease of concentration.

4. A representative sample of the diluted indicator must be obtained from the flow stream. Sampling from peripheral arteries low sampling rates, and large-bore, long, high volume catheters all contribute to distortion of the curve; a matter of even greater importance in computing mean transit time for calculating the volume traversed than for cardiac output. Another problem is associated with variable flow. A steady flow during the indicator dilution is assumed. If this is not possible, the sampling rate must be proportional to the flow rate. Bassingthwaighte et al (4) have reviewed the literature and provided evidence that fluctuations at the frequency of the heart rate introduce negligible error. Those at the respiratory frequency can introduce errors in estimated mean flow nearly as large as the peak-to-peak fluctuation in instantaneous flow. Setting up situations for slow respiratory patterns or calculating the average of several determinations provides a solution to this problem.

5. An accurate determination of indicator concentration must be made. As discussed above, albumin or plasma should not be added to the concentrated dye for stabilization. The geometry of the cuvette for stable light path length and width, adequate washout and stable erythrocyte orientation are important. Unusual requirements are present for densitometry of blood, since the background optical density of the erythrocytes in the blood will be 1 to 2 units, while the peak change due to the dye may be only 0.1 unit, or less. Stability of baseline and sensitivity of the densitometer are obviously needed. Miniaturization often leads to less accuracy. With a dye having as complex an absorption spectra as indocyanine green, it is essential to use a highly monochromatic light source if Beer's Law is to be

followed (10). It is clear that diluting the dye into water gives unexpected and unreliable results. Simmons and Shephard (11) have reviewed the controversy concerning the degree of non-linearity of densitometer read-out to indocyanine green dye concentration in blood. They present evidence of non-linearity for dye in plasma and, more important, for dye in blood. We and others have found minimal non-linearity using indocyanine green. Edwards et al (10) reported a 6% deviation over the range of 0 to 30 mg/L. Gathje et al (12) found 1 to 6 mg/L as the acceptable range.

Sutterer et al (13) found that heparin anticoagulant solutions containing sodium bisulfite cause a significant and erratic decrease in absorbency and so invalidate the calibration. Beware!

It is incumbent upon each user to calibrate the system at the time of each experiment, using the subject's blood. A sample with diluent but no dye and samples containing concentrations somewhat above the peak expected and a value between, e.g., 1/2 full scale, are needed to check linearity and system stability, and to give the calibration factor. At intervals an extended study of linearity is in order to check both the instrument and one's technique. Whereas repeatability of ± 5% (S.D.) may be expected, gross inaccuracies and high variability will be present using poor techniques or inadequate equipment. As with so many bioinstrumentation procedures currently in use, pitfalls await the unwary and ignorant. Nonetheless the use of indocyanine green dilution has been, and will undoubtedly continue to be, widely and successfully used, for most of the errors can be readily minimized.

SUMMARY

Chronically implanted flow transducers should be calibrated in vivo for maximum accuracy of measurement. Indicator dilution techniques are acceptable and commonly applied calibration procedures. This paper summarizes the principles of indicator dilution and reviews some of the recent developments, with emphasis on the assumptions which must be met and pitfalls to be avoided.

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12. SURVEY OF DIMENSION TRANSDUCERS

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Measurements of the size of an organ—its length, breadth, volume, etc.—can be especially revealing in studies of the cardiovascular system. Along with force, charge, and time, length is one of the four fundamental physical variables from which virtually all others can be derived (1).

The simplest way of estimating size of a structure is to compare it with some convenient yardstick. A physician may describe an enlarged liver, for example, as being detected because its edge can be palpated "two fingerbreadths below the right costal margin," a measurement which becomes significant if the liver edge cannot usually be felt at all, or if it has not been palpable before and is now. The units, "fingerbreadths," are crude and vary from one observer to the next, but are usually adequate for the purposes of the examination. The measurement technique demands a skilled observer, but his technique is always handy and easily employed.

Perhaps one step up in sophistication might be to use a ruler, scaled at appropriate intervals (again, appropriate to the needs of the examiner). Here one makes a visual comparison between a series of reference distances and the unknown one until he decides which set is closest: with a tape measure, he may decide an infant's head circumference is 35.1 cm because the tape end lies closer to that millimeter ruling than to any other. We use this sort of measurement in obtaining numerical data from an oscillograph record; it is worth mentioning here that most observers can train themselves to read a record to the nearest *tenth* (plus or minus a tenth, standard error) of the smallest unit on a scale, far better than we usually appreciate. Parallax, anticipatory errors, and other sources of observer error (including bias) must be eliminated to obtain the maximum resolution and accuracy, obviously, since visual comparison and judgment are always involved in this sort of measurement.

If a ruler and visual comparison are not accurate enough, we may choose to employ some sort of micrometer (from the Greek "mikros", small

or petty, and the Anglo-Saxon "metan" to measure (2). The most familiar of these is the micrometer caliper, which has a calibrated screw by which very small linear motions are translated into larger radial motions which can be discriminated much more easily. The usual method for using these, at least when applied to relatively incompressible objects, is to advance the screw until it touches opposite faces of the object and the resistance of the faces causes the screw to slip, making an easily recognized clicking sound as the advancing mechanism is disengaged. A resolution of about a thousandth of an inch (.001", or 25 micra) is obtained easily with inexpensive calipers.

All of these techniques are non-electronic, require a somewhat skilled observer, and their application in chronic animal studies is limited. In general, the more useful techniques for obtaining physiologic information from chronically instrumented animals require greater sophistication and the introduction of some source of energy—electrical, wave energy, etc.—into the system under examination. If a change in organ dimensions occurs in some measurable way the energy flowing through the system, this can be used to determine and record dimensions. Devices capable of measuring length or changes in length are generally termed *strain gages.* An excellent discussion of several types was presented by Peterson (3), from which much of this description is drawn.

RESISTANCE, CAPACITANCE, INDUCTANCE

The simplest resistance strain gage used in bioinstrumental measurements is the mercury-in-rubber gage first described by Glaser but made popular by Whitney (4). It consists of an elastic, small-bore tube filled with mercury in an electrical circuit connected to a source of electrical current. The resistance of the tube (usually on the order of a few ohms) varies with its length, since elongation increases the length of the current path and reduces the cross-sectional area of the mercury column; though the basic transfer function between length and resistance is nonlinear, the device is sufficiently linear over limited strains (± 20%, for example) for use in a variety of measurements. Whitney originally used them to substitute for volume plethysmography in the limbs, and Rushmer and co-workers (5, 6) employed them to measure ventricular and aortic dimensions in acutely and chronically instrumented animals. While easy to construct and use, unfortunately they are temperature-sensitive, fail (probably due to fluid leakage and corrosion) in days to weeks when used chronically, are difficult to calibrate in use, and—because some force is needed to lengthen them, however slight—tend to restrict the motion of the organ under examination.

Other resistive gages, bonded and unbonded, have been used to measure

the size of cardiovascular structures. Irisawa and co-workers (7) designed a partial "cuff" to fit around large veins, which would change its curvature as the vessels changed size, lengthening or shortening the wire gages mounted on the surface of the cuff. Feigl and Fry (8) employed an ingenious mechanical structure with a similar approach in order to measure left ventricular thickness which might, with considerable modification, be used to measure wall thickness in chronically instrumented animals. Several investigators in Peterson's group (3) have attempted to design a catheter-tip gauge for estimating changes in arterial diameter.

Determination of capacitance between two plates sutured to opposite sides of an organ could, in principle, be used to determine changes in the organ's size. Such techniques are complicated by changes in the dielectric behavior of the tissue, intricate current paths through the body, resistance effects, etc., and are more appropriately considered as impedance techniques (see below), since those effects usually dominate the measurements obtained.

Variable inductance has been used in several forms to measure changes in cardiac and vascular dimensions in chronically instrumented animals. Mutual inductance, in which the coupling of an electromagnetic field from one coil to another is used to estimate changes in their spacing, is described in more detail elsewhere in this Symposium. Variable inductance, in which one coil is attached to one side of the organ and a ferromagnetic slug is attached to the other, has been used to estimate change in intraventricular diameter (9), since the coil inductance will rise and fall as the slug moves into and out of the coil. Both these techniques, unfortunately, suffer from problems in calibration, and moreover possess a nonlinear transfer function between spacing and output which complicates their use. They do offer the advantage of not requiring a mechanical linkage between the two transducer elements, however, which minimizes the force applied to the organ.

The differential transformer, which resembles two inductance gages, is far more linear. Three coils, one generating an electromagnetic field and the other two (arranged in opposition) detecting changes in it, interact with a slug which moves up and down inside the coils. The technique is exquisitely sensitive and linear over a range roughly equivalent to the length of the coils; elegant miniature devices have been constructed by Pieper for measurement of aortic (10) and ventricular diameters (11) by means of catheter-tip "feeler gages". The Rushmer group (9) also explored their use for continuous determination of intraventricular diameter in conscious dogs.

IMPEDANCE

The electrical impedance between two electrodes introduced into an

organ will often vary as its dimensions vary. This observation has been used by a variety of investigators to attempt to measure many cardiovascular variables, since changes in impedance at a rate coincident with the heart rate are often detected.

Determination of impedance is, basically, quite easy (12). Using relatively simple electrode "transducers"[1], the impedance to high-frequency current (100 kHz) flow is measured. Impedance will rise as the electrodes move farther apart, as the cross-section of the tissue decreases, or as the resistivity of the material changes. More accurate measurements are obtained by using four electrodes, the outer pair to generate a constant current and the inner to sense the voltage drop through the tissue.

Unfortunately, many variables influence the impedance between a pair of electrodes. For example, if one places electrodes across the left ventricle one might expect the impedance to fall during systole as the distance between them is reduced; in practice, impedance rises because it is strongly influenced by the bulk conduction of blood in the ventricle, and during systole this blood volume is reduced (13). Calibration can become virtually impossible, since changes in shape are sensed as well as changes in dimensions.

SONIC

Use of high-frequency sound, or ultrasound, offers many advantages in determining biologic dimensions. In general, two pulsed ultrasound techniques have enjoyed some popularity: (1) determination of the time required for a burst of sonic energy to pass from one piezoelectric transducer to another (sonomicrometry) (14), or (2) determination of the time required for a burst of sonic energy to pass from a piezoelectric transducer to a reflecting surface and back again (sonar, or echo-ranging) (15). Continuous-wave techniques have been explored but are far more difficult to use (16).

The use of ultrasonic transit-time to determine changes in ventricular diameter in conscious dogs was first described by Rushmer *et al* (14), but their "sonocardiometer" was relatively complicated and the technique never became popular despite simplification of the circuit design (17) and development of techniques for intraventricular implantation (18).[2] Since—at least for the laboratory comfortable with more sophisticated instruments—it has much to recommend its use in measuring changes in biologic dimensions, it will be described in some detail here.

[1] Since they do not transform energy from one kind to another, "transducer" is inappropriate though commonly used terminology.

[2] The term "sonomicrometer", suggested by Rushmer in 1965 (19), has come to replace the term sonocardiometer used earlier because the technique can be employed in many organs other than the heart.

The principle of the sonomicrometer is quite straightforward. Two piezoelectric transducers are sutured to opposite sides of an organ; one is excited with electrical pulses to produce acoustical bursts which pass to the second transducer. The associated electrical circuits are all designed to measure the time required for an acoustical burst to travel this distance and to convert that measurement into a voltage suitable for recording on an oscillograph.

The time required for the sound burst to arrive at the second crystal is the distance between them divided by the velocity of the sound in the tissue; fortunately, the velocity of sound in body tissues is about equal to that in water (1.5×10^5 cm / second, or 1.5 mm / μsec) except for fat (1.44 mm / μsec) or bone (about 3.6 mm / μsec), and thus the ultrasonic transit-time is directly proportional to the distance between the transducers. It is this feature of dependence on a single physical variable that is the principal advantage of the technique. Sound velocity varies little with temperature and not at all with time, and thus drift is not a basic problem. Since precalibrated crystal pairs seperated by a known acoustical delay can be substituted for those in the animal, repeated and accurate calibration of the record is easy. The resolution can be quite high (the minimum resolution during proper operation is ¼ wavelength, which for 5 mHz sound is about .07 mm), and small changes in transducer spacing are easily detected and recorded. The linear range of measurement is quite large, and can be further expanded and optimized by changing the resonant frequency of the transducers used. The transducers can be quite small, are easily introduced surgically, require only three or four wires, and are not physically linked to each other during the measurement. The overall frequency response of the instrument is limited only by the repetition rate of the pulse, which for distances of 100 cm or less can be almost 1000 / sec. Devices can be built for about $50 by a moderately skilled electronic technician, and since they use integrated circuits, the layout is not critical. The potential transducer lifespan in chronically instrumented animals appears to exceed six months.

Unfortunately, the technique is not as easy to use as one might desire. First of all, the sound fields generated by these small transducers are highly directional and, even when broadened with acoustical lenses, the amplitude of the pulse detected by the second one may be too small for the instrument to "track". This is a mixed blessing, in one sense, for sometimes improper transducer placement—as in measuring intraventricular diameter, for example—can be easily detected since the device cannot be forced to operate. For application in which this is a less desirable feature, lower frequency operation, curved transducers, and better lenses can be used to improve one's chances of getting the instrument to function. The oscillo-

scope which must be used to insure correct functioning of the instrument can be an expensive one, since a two-channel 'scope with good (up to 10mHz) response is needed. Perhaps because of the necessity for experimenter experience in using the technique, and perhaps because the market for instruments is limited, no commercial supplier of devices or transducers has appeared.

Recently Bishop (see elsewhere in this Symposium) has described a technique for mounting ultrasonic transducers near the end of a cardiac catheter which can be introduced into the left ventricle to measure intraventricular diameter; we have used a more complicated structure on a catheter-tip for measurement of aortic and carotid artery diameters (20). In both cases the accuracy and frequency response of the devices is limited only by the construction details of the catheters and materials, which must be established before they can be used with confidence.

Ultrasonic pulse-echo detection has been somewhat more popular but its use appears to be somewhat different. Its principal advantage over sonomicrometry is the fact that only one transducer is needed, and since tissues are relatively transparent to ultrasound the transducer can be placed on the skin and echoes from structures within the body detected. A number of investigations of changes in cardiac (21) or vascular size (22) in man have been carried out in this way. Those experienced with the technique usually find the major limitation is difficulty in identifying and following echoes from the interface they are seeking, and its use in chronically instrumented animals has been quite limited. Though not explored, one might profitably develop techniques in which a highly reflective interface (an air-water interface, for example) could be introduced at surgery similar to that in sonomicrometry; this interface, which would require no electrical connections, might be easily tracked with pulse-echo methods for determining changes in chamber or vessel size. One should note here the obvious fact that the instrumental advantages of sonomicrometry apply to sonar as well, and that the calibration of the devices must include the fact that the time for pulses to reach an echoing surface and return to the original surface is proportional to twice the distance between them. Transducers on catheters offer promise of determining cardiac or vessel chamber size without surgical exposure.

OPTICAL

There are virtually no applications of optical measurement techniques used in chronically instrumented animals. A major limitation on such approaches is the limited penetration of optical energy through tissue, and

thus their use in cardiovascular measurements is usually limited to vessels which can be visualized (23, 24), which is generally not the case in chronically instrumented animals. The techniques available via laser technology today, capable of resolving very small changes in much larger distances with a great deal of accuracy, would offer many advantages for the bioinstrumentalist should this limitation be overcome.

X-RAY

A favorite technique for determining the dimensions of organs under the skin is X-ray. To be useful, a sharp distinction in X-ray absorption must be present naturally or be introduced; to this end radiopaque fluids can be introduced into the cardiovascular system or lead beads or other markers (discussed elsewhere in this Symposium) can be used to define margins of interest. The principal limitation of such techniques is the necessity of using bulky, expensive X-ray sources and detectors (film or fluoroscopic tracking of these margins), which necessitates restraint or anesthesia during the determination in "chronically" instrumented animals. Radiation dosage and resolution further limit these applications (a brief description of X-ray resolution can be found in reference 25). X-ray offers the major advantage of not requiring surgical exposure in order to make the measurements, a distinct advantage in assessing normal size and changes in size of cardiovascular structures in intact animals since anesthesia and surgical exposure can appreciably change their mechanical properties (25) or the physiologic state of the animal (26).

SUMMARY

A variety of instrumental techniques for determining dimensions of organs in chronically instrumented animals is available. Perhaps the most useful, when surgery can be tolerated, are those employing ultrasound, but they have been limited to a few laboratories. As always, the demands of the experimental situation for accuracy, and the demands of the experimenter for utility, should dictate the choices that are made.

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13. THE ULTRASONIC PULSE TRANSIT TIME TECHNIQUE[1]

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The nondestructive transmission of ultrasound within a living tissue demands that some compromises be made with regard to the power used. The ultrasonic frequency requirements of any given technique invariably place some limitations on both the sensitivity and selectivity of the measurement system. With regard to diagnostic ultrasound, the most common frequencies in use range from 2 to 10 mHz. In general, at least insofar as pulsed ultrasonic dimension measurements are concerned, the lower frequencies sacrifice selectivity for sensitivity. In the measurement of the internal dimensions of the cardiac ventricles, a short burst of ultrasound transmitted from one endocardial surface can be detected on the opposite surface if properly amplified. The basic technique along with details for the construction of transducers to accomplish this are related below.

In the pulse transit time technique for measuring intraventricular dimensions (1), a short burst of ultrasound is transmitted between a pair of transducers from one endocardial surface to the opposite one. After appropriate amplification and signal conditioning, a voltage proportional to the transit time or distance measured can be recorded on an oscillograph. The velocity of ultrasound in most body tissues, with the exception of bone and fat, is 1.55×10^6 mm/sec and is approximately equal to the velocity of ultrasound in water. Thus, to calibrate the recording in terms of distance in millimeters one has to obtain a recording between two piezoelectric crystals separated by a known distance. This can be accomplished by placing piezoelectric crystals at various fixed distances across a Lucite block milled to different thicknesses (1). The transit time for each pair of piezoelectric crystals can be accurately measured with a calibrated oscilloscope and the

[1] Supported, in part, by USPHS (NHI), grants He-12415-01 and HE-14355-01.

corresponding distance calculated. Since the output of the sonomicrometer is linear, only two distances are required to calibrate a recording (Fig. 1). However, to provide for the range in diameters encountered in canine ventricles, one should have calibrations ranging from 15 mm to 50 mm (1, 2).

To assure minimum measurement error and ease of placement, the transducers should be kept as small as possible. It is plain that a point source on both the transmitter and receiver ends would minimize error as the angle between the two transducers shifts with the movement of the endocardial surface. However, power and signal to noise requirements, both dependent upon the distances to be measured, necessitate a larger transducer size for canine internal left ventricular diameter measurements.

For measurements in the 2 to 4 cm range, distances which are most often present within the dog heart, a ceramic piezoelectric material resonant at 5 mHz in the thickness mode can be used (LTZ - 2, Transducer Products, Inc., Torrington, Conn. 06790). The material is supplied in 1 inch squares and is cut to shape using a carbide-tipped scriber. A number of 5 mm circles are scribed into each square, and then each circle is broken from the square

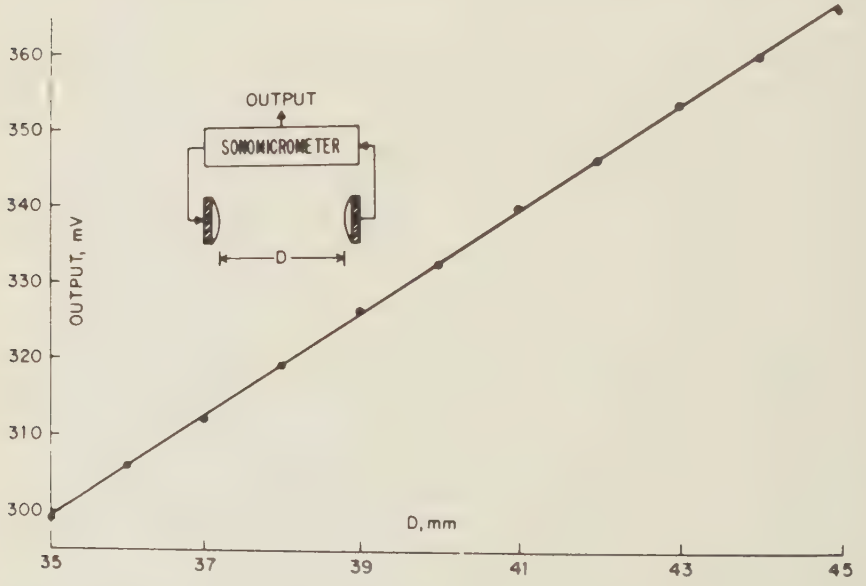

Fig. 1. Calibration of complete sonomicrometer system with transducers submerged in water. Note the linear relationship between output and distance. Reproduced, by permission, from the *Journal of Applied Physiology* 23:292, 1967.

using a small sidecutter. A small hole is drilled through the center of each circle using an abrasive cutter (S.S. White). An area ½ mm square is polished on each side of the disc at the edge of the central hole using the edge of a scalpel blade, until the protective coating is removed and the bright plating underneath can be seen. The cleaned areas are then tinned with a low melting point solder, using noncorrosive liquid flux and a 3 watt soldering iron. The piezoelectric material is extremely temperature sensitive and exposure to temperatures above 150°C for more than a few seconds can depolarize it, rendering it inactive. To each pretinned area is soldered the tinned end of one of a twisted pair of multistranded highly flexible wires (Superflex, 29AWG, Calmont Wire and Cable, Inc., Santa Ana, California 92707).

Using a cork borer, a 5 mm circular disc of expanded polystyrene is cut from a disposable coffee cup and flattened to a thickness of approximately 2 mm. After boring a hole in the center of the polystyrene disc with a hypodermic needle, the disc is slipped onto the free end of the lead wires and potted in place at the base of the ceramic disc using a quick curing epoxy. With the transducer held upward, a semispherical polyester lens is cast in place on the flat ceramic upper surface by applying a catalyzed liquid (Clear Cast, American Handicrafts Co.) to the surface, a drop at a time, to attain a rise of approximately 2 mm at the disc's center. After 24 hours the lens is cured and the whole assembly dip-coated in a clear protective film (TE-10, Insul-X Product Corp., Yonkers, New York). A schematic of the transducer is shown in Figure 2.

The transducers used in our laboratory (M and M Transducer, 4006 Belle Grove, San Antonio, Texas) range from 2 to 5 mm in diameter, depending upon the size of the animal's heart. The size of the transducers, as mentioned earlier, is critical to the interpretation of the actual dimension recording. The ultrasound travels between the transducers in a narrow beam which is a function of the dispersion ability of the lens and the diameter of the piezoelectric crystals. Within certain limits a small transducer will transmit a narrow beam of ultrasound. Thus, if a tracking signal is obtained by the receiving transducer, one is assured of good alignment and an accurate measure of the distance between the crystals in the plane of implantation. This is one of the advantages of the ultrasound technique for measuring distances. These criteria would not be met by large transducers or low frequency ultrasound, since the transmitted beam of ultrasound would be more widely dispersed. Under such conditions, the diameter measurement could include not only the perpendicular distance between the crystals, but also lateral and vertical movement of the ventricular walls. In addition, one would be uncertain whether the transducers were placed in a plane perpen-

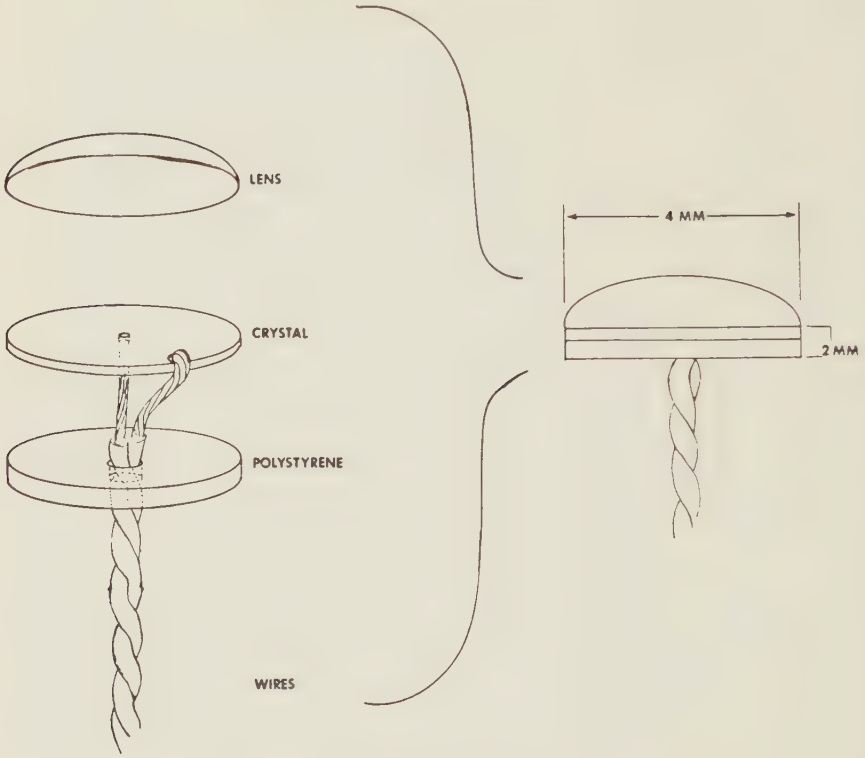

Fig. 2. Schematic of finished sonomicrometer transducer as described in the text.

dicular to the longitudinal axis of the left ventricle, seriously impairing the potential physiologic significance of the record obtained (2-4).

SUMMARY

This report describes the basic principles and the details of transducer construction for measurement of the internal dimensions of the cardiac ventricles.

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14. LEFT VENTRICULAR DIMENSIONS DETERMINED BY BIPLANE CINEFLUOROGRAPHY OF CHRONICALLY IMPLANTED RADIOPAQUE MARKERS: CRITIQUE OF THE METHOD[1]

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Angiocardiographic techniques provide reasonably accurate estimation of left ventricular dimensions and volumes (1). In general, the volume of the left ventricular cavity can be calculated most accurately by representing the left ventricle mathematically by a nonprolate ellipsoid whose axes are directly measured from the contrast-filled ventricle. Applying these principles, a technique has been developed to measure similar ventricular axes without necessitating the introduction of contrast material. The method requires implantation of six radiopaque beads which define the axes of an assumed ellipsoidal shell of muscle near the endocardium. The details of this method are available elsewhere in this Symposium (2); this presentation will consider the accuracy of this approach for assessing ventricular dimensions.

It is first necessary to show that known spatial distances can be measured accurately from biplane cineradiographs. To this end the three axes of an ellipse were constructed with sticks, each with lead beads secured at their ends. The ellipse was suspended in front of the biplane cinefluorograph and films exposed as the ellipse was rotated (Figure 1). A lead ball of known diameter was filmed for calibration and the data processed. Table 1 shows the results. Mean data for ten consecutive frames are shown. Accuracy to within 1 mm for each axis and less than 1 ml for calculated volume is evident. The narrow range for axis values reflects the high degree of reproducibility possible with the method.

Reproducibility in measuring physiological data from day to day is also required. This has been tested repeatedly. One such study, in Figure 2, illustrates calculated ventricular volumes measured from the same film on separate days. Comparing day 1 and 2, the correlation coefficient of 0.99

Fig. 1. Three axes of an ellipse constructed of sticks and radiopaque beads are shown in the left panel. The right panel contains a frame from the 35-mm cineradiograph of the stick figure.

TABLE 1

	L_1[1] (mm)	L_2[2] (mm)	L_3[2] (mm)	Volume (cc)
Actual Values	60.1	30.5	30.5	29.6
Calculated Values				
Mean (n = 10)	59.9	31.5	29.9	29.5
Range	59.8-60.0	31.4-31.6	29.6-30.1	29.3-29.7
SD	0.08	0.07	0.15	0.14

[1] The long or major axis of the constructed figure.
[2] One of the two short or minor axes of the constructed figure.

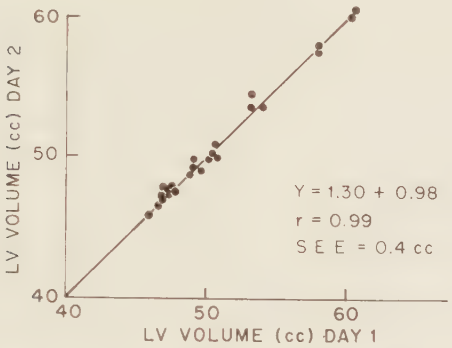

Fig. 2. The reproducibility of volume measurements is illustrated. Ventricular volume data digitized on day one are shown on the horizontal axis and those from day two on the vertical axis. One cardiac cycle is plotted so that volumes vary from large to small. The line of unity is drawn. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

and the standard error of the estimate of 0.4 ml indicate excellent reproducibility.

Turning to the measurement of physiological variables, how accurately does the method measure true ventricular volumes? Both end-diastolic and end-systolic volume are overestimated. While direct studies in the same heart have not been made comparing end-diastolic and end-systolic volume measured from implanted beads versus cast or angiographic volumes, this conclusion seems certain, based on published angiographic volumes for anesthetized intact dogs. Hallermann et al (4) reported a mean end-diastolic volume of 19 ml/10 kg and end-systolic volume of 6.9 ml/10 kg in anesthetized closed chest dogs. Similarly, Bartle and San Marco (5) found a mean end-diastolic volume of 21.1 ml/10 kg and end-systolic volume of 11.3 ml/10 kg. For comparison, recent studies with the implanted bead technique in 8 anesthetized closed chest dogs revealed an average end-diastolic volume of 36 ml/10 kg and end-systolic volume of 25 ml/10 kg (6). This overestimation of absolute volume is to be expected since it is recognized that a rim of endocardial muscle including the trabeculae carneae and papillary muscles lies between the beads and ventricular cavity and is therefore included with the cavity in the calculation of absolute volume.

Stroke volume, on the other hand, is measured with excellent accuracy. In 20 open chest animals, stroke volume was obtained simultaneously with an electromagnetic flow probe around the ascending aorta and by the implanted bead technique. The results are shown in Figure 3. A significant correlation ($r = .92$) is evident.

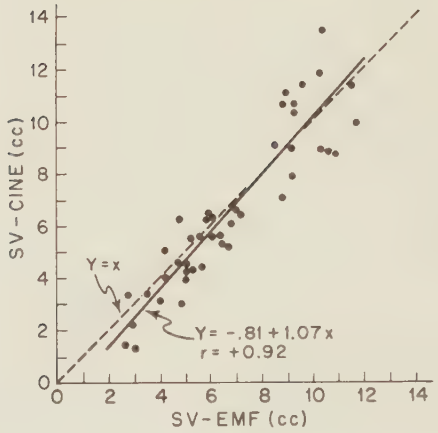

Fig. 3. A comparison of stroke volumes obtained simultaneously by an electromagnetic flow probe around the ascending aorta and the bead technique. Bead stroke volume is on the vertical axis, electromagnetic flow probe (EMF) stroke volume is on the horizontal axis. The equation for the data points is drawn as a solid line; unity is the dashed line. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

It is important to indicate that the cine stroke volumes plotted in Figure 3 are calculated as the left ventricular volume lost from the initiation of ejection to the end of ejection as determined by the simultaneously recorded flow probe signal. This is necessary because there is a consistent decrease in left ventricular volume observed during the isovolumic phase of contraction which is not part of the forward stroke volume. In a recent analysis of 43 beats from 7 conscious dogs, this decrease in volume averaged 5% of the end-diastolic volume. Others have reported similar decreases in left ventricular dimensions prior to aortic valve opening in dogs using a sonomicrometer technique for measurement of an internal diameter (7) and recently in man with a cineangiographic analysis (8). It has been suggested that this apparent loss of volume occurs as a result of posterior movement of the mitral valve. In this regard it is of interest that a 4% average apparent increase in left ventricular volume was observed during isovolumic relaxation in the same 43 beats which showed a 5% loss of volume during isovolumic contraction. Anterior displacement of the mitral valve prior to its opening may account for this observed volume increase.

The sensitivity of the method for following beat to beat changes in ventricular volume has been examined. Since end-diastolic compliance of the left ventricle remains unchanged during most experimental physiological maneuvers (9-11), comparing beat to beat changes in end-diastolic pressure and volume provides a means of determining if directionally appropriate changes in volume can be detected. This was done using data from a recent study of the transient effects of a sudden increase in heart rate on left ventricular dimensions (12). In this study 6 open chest dogs, with dimension markers in their left ventricles and aortic pressure and cardiac output controlled, were studied during an abrupt increase in heart rate. Each dog was studied at 3 levels of cardiac output. Beat to beat changes in mean end-diastolic pressure and volume from 18 studies for 3 beats before and 12 beats after heart rate was raised are shown in Figure 4. In the first beat after increasing heart rate end-diastolic pressure was decreased. It was slightly but statistically significantly higher in the next beat and then fell progressively. End-diastolic volume behaved identically including a small statistically significant increase in volume on the second beat after the heart rate was raised.

The sensitivity of the bead dimension technique to beat to beat changes in stroke volume was examined using data from a recent study of the effects of acetyl strophanthidin in conscious chronically instrumented dogs (13).

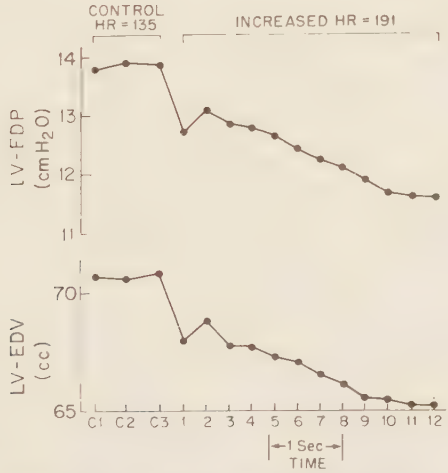

Fig. 4. Beat-to-beat changes in mean end-diastolic pressure (upper panel) and end-diastolic volume (lower panel) from 18 studies in 6 dogs where heart rate was abruptly increased. The average heart rate before and after the change is shown at the top. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

Stroke volume was simultaneously available from an ascending aortic electromagnetic flow probe (Statham Instruments, Oxnard, California) and the biplane films of the dimension markers. Small beat to beat changes in stroke volume occur because of respiratory variation and the variability of the interval between beats (sinus arrhythmia) present in conscious dogs, both before and after acetyl strophanthidin. The comparison of flow probe and dimension stroke volume from one dog is shown in Figure 5. It is evident that in addition to a close estimation of absolute stroke volume by the dimension method, small beat to beat changes are also detected. A significant correlation was found ($r = 0.89$). This was one of 7 similar analyses where the average correlation coefficient was 0.87 with a range of 0.77 to 0.93.

Ventricular dimensional data can be used to examine ejection rates or changes in geometry during the cardiac cycle. Accordingly, it is important to determine if this method accurately describes the instantaneous changes in ventricular volume during a single beat such that changes in ejection rate, for example, are detectable. Again, data from conscious instrumented dogs

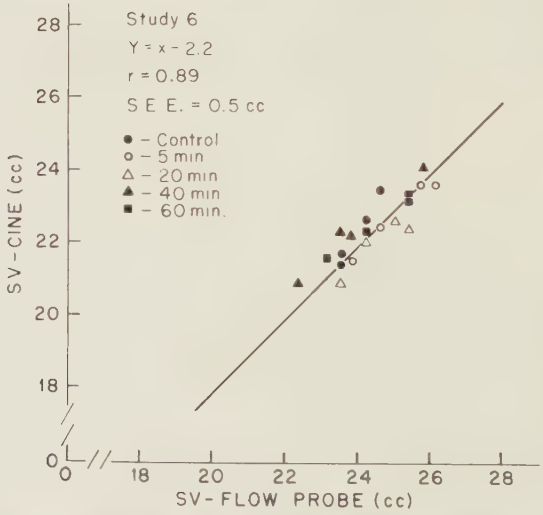

Fig. 5. The relationship between stroke volume measured simultaneously with an electromagnetic flow probe on the ascending aorta (horizontal axis) and from biplane cinefluorographs of the implanted markers (vertical axis). Each point represents one beat. Data from a control state and periodically following intravenous acetyl strophanthidin are plotted. The regression line for all the data points is drawn. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

given acetyl strophanthidin were examined. Along with the simultaneous recording of the cineradiographs and flow probe signal was a cine frame marker which allowed temporal correlation of data. It was thus possible to examine and compare in a single beat the amount of blood ejected every 16.7 msec (1/60 sec). This type of analysis for a single beat before and after acetyl strophanthidin is shown in Figures 6 and 7. It is evident that changes in instantaneous ejected volume (Figure 6) and cumulative ejected volume (Figure 7) as described by the flow probe are nearly identically reproduced by the dimensional method. Changes in both the rate of change of volume as well as absolute volume were detected by the cinefluorographic measurements. To quantify this type of analysis, the per cent increase in ejection rate after acetyl strophanthidin was calculated from both the flow probe and the dimensional data in 6 dogs (Figure 8). The latter was calculated as the maximal slope of the ejection portion of the plotted ventricular volume curve. The correlation coefficient of 0.872 indicates that this method follows instantaneous changes in dimensions with an accuracy sufficient to detect relatively small alterations in ejection rate.

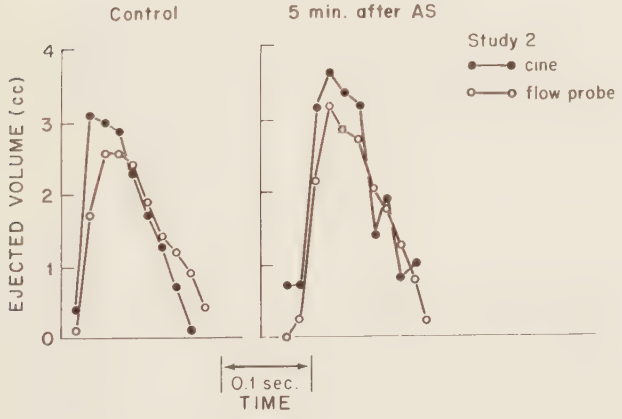

Fig. 6. The changes in ejected volume each 16.7 msec (1/60 sec) are plotted for one beat before (left panel) and one beat 5 minutes after acetyl strophanthidin (right panel). The cinefluorographic (dots) and flow probe (circles) data were obtained simultaneously. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

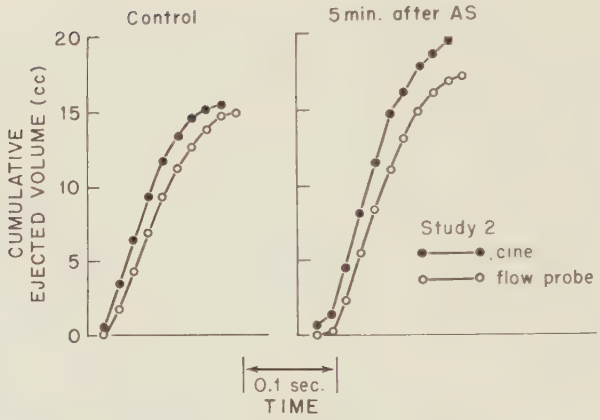

Fig. 7. The changes in cumulative ejected volume during a single beat. These are the same data and format shown in Figure 6.

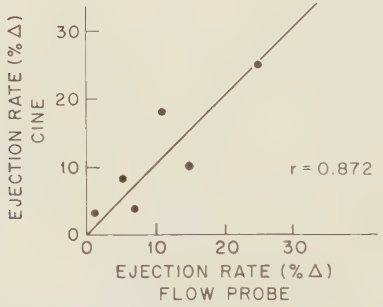

Fig. 8. A comparison of the per cent change in ventricular ejection rate after acetyl strophanthidin calculated from the aortic flow probe data (horizontal axis) and the cinefluorographic data (vertical axis). The correlation coefficient is 0.872. The line of identity is drawn.

SUMMARY

A critique of a method for determining three ventricular dimensions with biplane cinefluorography has been presented. This method overestimates absolute ventricular volume but accurately assesses stroke volume. Additionally, the method is sensitive to beat-to-beat changes in volumes as well as instantaneous changes in dimensions during a single contraction.

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15. MEASUREMENT OF DIMENSION BY INDUCTANCE COILS[1]

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Several inductance methods have been developed to measure mechanical displacement. This parameter has advantages not offered by capacitance or resistance as it does not require mechanical contacts and is not affected by the dielectric qualities of the surrounding medium. The differential transformer, employing a movable sensor coil placed between two mutually opposing excitor coils, enjoys wide popularity due to its excellent displacement-output signal linearity (1). It is, however, unsuitable for chronic cardiovascular implantation because of the awkward center position of the sensor coil, high actuating force, and the large mechanical assembly required to hold the three coils in position. This assembly becomes quite large for typical cardiac dimension changes, as the total coil length must be approximately five times the dynamic displacement range.

A single-coil displacement transducer may be formed from a sliding metal core within the longitudinal axis of a tubular coil. While this variable inductance method has been used successfully to produce an intraventricular dimension gauge (2), it presents problems in construction, installation, and biological disturbances. This type of gauge does offer mechanical stability, resulting in an exact measurement of the desired dimension.

For minimum biological interference, the gauge should take the form of two separate components which measure the distance between their respective inner surfaces. This physical discontinuity across the measured distance is satisfied by two identical miniature coils which function as a transformer with variable primary-secondary spacing. One of the coils, designated as the primary, is energized with an alternating-current signal, producing a magnetic field that induces a voltage in the nearby secondary coil. The amplitude of this voltage, V, is proportional to the inverse cube of the distance, D, between the coils, or $V = K/D^3$, where K = a constant. This relationship, shown as curve A, Figure 1, has been verified by an analysis of the characteristics of coaxial cylindrical coils separated by a distance much

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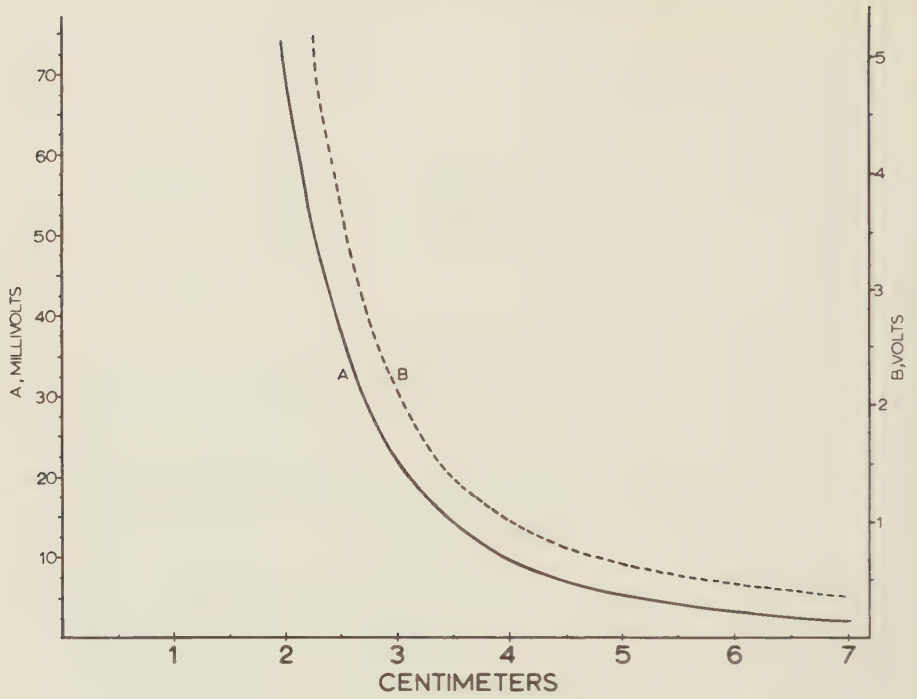

Fig. 1. Relationship between coil spacing and output voltage. Curve A, millivolts AC output from secondary coil with 30 volts p-p, 10 KHz, across primary coil. Curve B, typical DC output from amplifier-demodulator. Reproduced, by permission, from *Biomedical Sciences Instrumentation,* Plenum Press, 1968.

greater than their winding thickness (3). While this response is nonlinear, it is usable in most cardiac measurements without elaborate linearization techniques (due to the small portion of the curve used).

The coils require very simple supporting circuitry, as shown in the block diagram (Fig. 2). A commercial oscillator may be used to supply the 10-30 KHz excitation, and a simple 1000X amplifier will increase the secondary signal to a level suitable for a diode rectifier-RC filter demodulator. The output will then be a high level DC signal, such as curve B, Figure 1, suitable for recording or display.

COIL SELECTION AND PREPARATION

The coils should have high inductance in order to provide a usable signal over a distance up to 10 cm without excessive driving power. They must also be as small as possible to limit biological trauma and undesirable

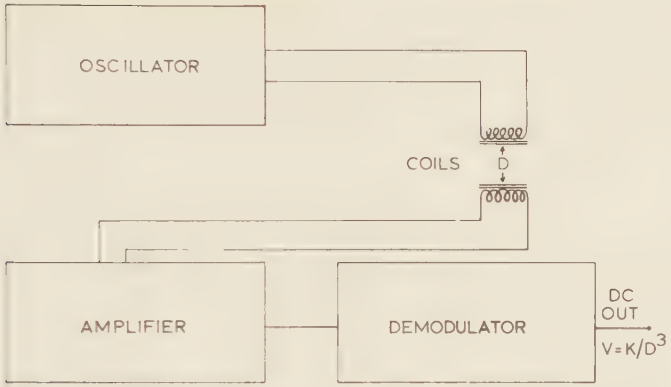

Fig. 2. The components for a single channel of dimension information. The oscillator should supply 20-50 volts p-p at 10-30 KHz to the 1000 ohm coil, and the amplifier should have a gain of approximately 1000. The demodulator is a rectifier - RC filter with suitable time constant. Reproduced, by permission, from *Medical Research Engineering* 8:4, 1969.

inertial effects. These requirements are best met by the Wabash Magnetics 432-8562 bobbinless coil made of 1500 turns of No. 48 wire. These coils, 2 mm in depth and 5 mm outside diameter, are fitted with an Indiana General 06 ferrite core (permeability 6000) to yield a 38 millihenry inductance. The displacement transducer formed by a pair of these coils has been used to measure left ventricular width in chronically instrumented dogs for periods up to one year (4). They have also had application in measurement of spleen thickness, small animal respiration, and mechanical displacements of instruments such as muscle pullers and motion detectors. Coil operation is affected only by large metallic obstructions or strong magnetic transients, and their general ruggedness in harsh environments is excellent if sufficiently protected.

Basic coil preparation consists of the attachment of Teflon insulated lead wires and the application of an epoxy covering. The wire and epoxy process has been developed to prevent the entrance of body fluids to the coil and to the soldered connection joining the lead wire to the coil wire. Extensive tests have revealed that the major fluid route is not directly through the epoxy coating but along the epoxy-wire insulation interface. This problem could be solved by using a wire insulation material which bonds to the epoxy, but the Teflon has been retained due to its vastly superior performance in long-term implants. The Teflon-epoxy interface has been made sufficiently waterproof by mechanically and chemically etching the insulation as described below, and extending the coil package (Fig. 3).

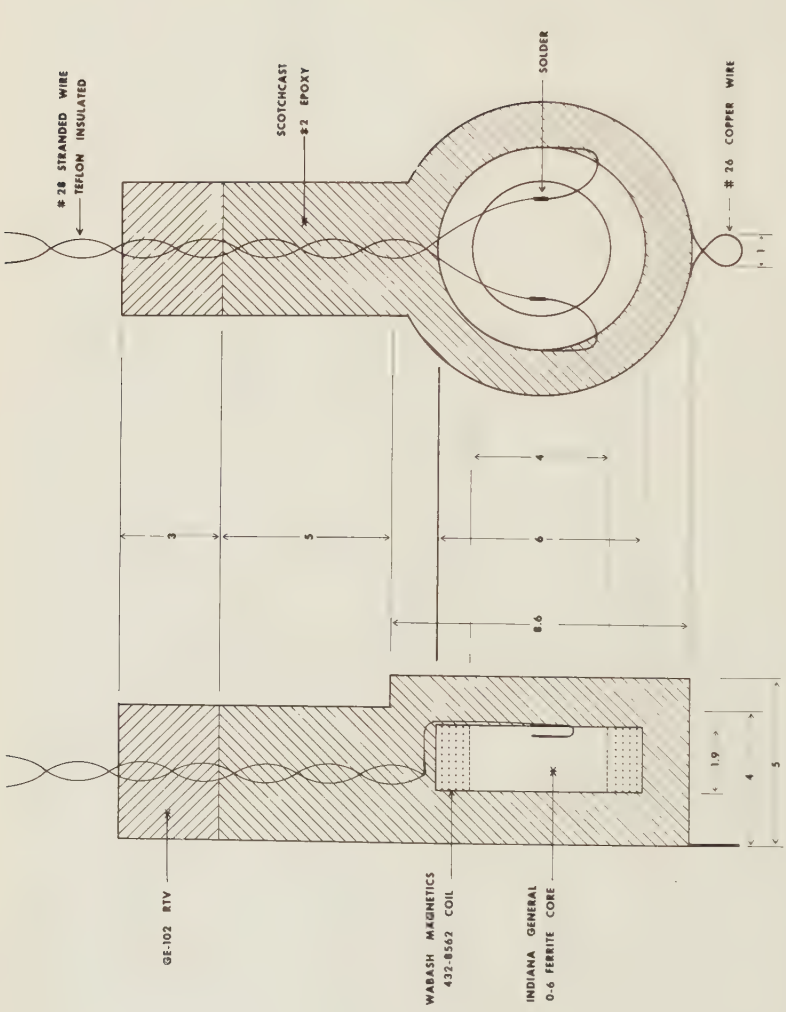

Fig. 3. Dimension coil assembly. The epoxy is molded around the coil and lead wire to prevent the entrance of body fluids. All dimensions are in millimeters.

The epoxy-wire exit extension lengthens the interface path the fluid travels toward the solder connection, and also retards movement of the insulation. Tests have shown that heart motion causes a pumping action which moves fluid along the interface, making a static soak test invalid for predicting coil performance in vivo. The RTV silicone rubber at the wire entrance helps reduce this effect, and distributes wire bending over a longer section to prevent breakage.

Scotchcast No. 2 epoxy, selected for its success in protecting human pacemakers, is molded around the coil by one pour into a paper form. This method seems superior to coating buildup by repetitive dipping, which produces a layering that enhances water absorption. The detailed procedure for this casting and wire preparation is as follows:

1. Dip the bare coil for one second in Scotchcast XR-5001 epoxy adhesion promoter, shake off excess and allow to dry. Carefully install core in coil, and repeat dipping. Check the continuity of the coil by measuring its 550 ohm DC resistance.

2. Twist No. 28 stranded Teflon insulated wire into 60 cm lengths. Roughen 1.2 cm of insulation at one end of each conductor with fine sandpaper and immerse the roughened section in Fluorocarbon Teflon etchant for 6 hours. Remove the etch residue with scouring cleanser, allow to dry, and dip the etched insulation in XR-5001 adhesion promoter. Remove 1.5 mm of insulation and tin the exposed wire.

3. Cut the wires extending from the coils to 3 mm and remove 1.5 mm of the enamel insulation by inserting the wire into a molten solder bubble. The solder should be just above melting temperature, and may be floating on a flat-tipped controllable soldering pencil. Bend the wires over the core and space 3 mm apart as shown in Figure 3. Solder the tinned lead wires to the coil wires and place the assembly on a level surface with connections upward.

4. Mix 5 cc of Scotchcast No. 2 epoxy according to directions, de-gas in a vacuum chamber, and allow to cure at 25°C for 1½ hours. Place a large drop of this epoxy on the soldered connections, securing them to the core and coil upper surface. Use only a large enough drop to cover the top of the coil. Allow to cure for 12 hours or more.

5. Construct the epoxy casting form (Fig. 4) from brown paper tape cylinders wound to the proper size on metal rods. Cement the cylinders together with Dupont Duco glue, allow to harden, and apply Krylon silicone spray to the form interior. Allow the spray to dry, and insert the coil into the form with the lead wires extending outward from the stem and the coil surface, parallel to the bottom of the form. Take extreme care not to damage the coil during this operation. Plug the wire exit with General

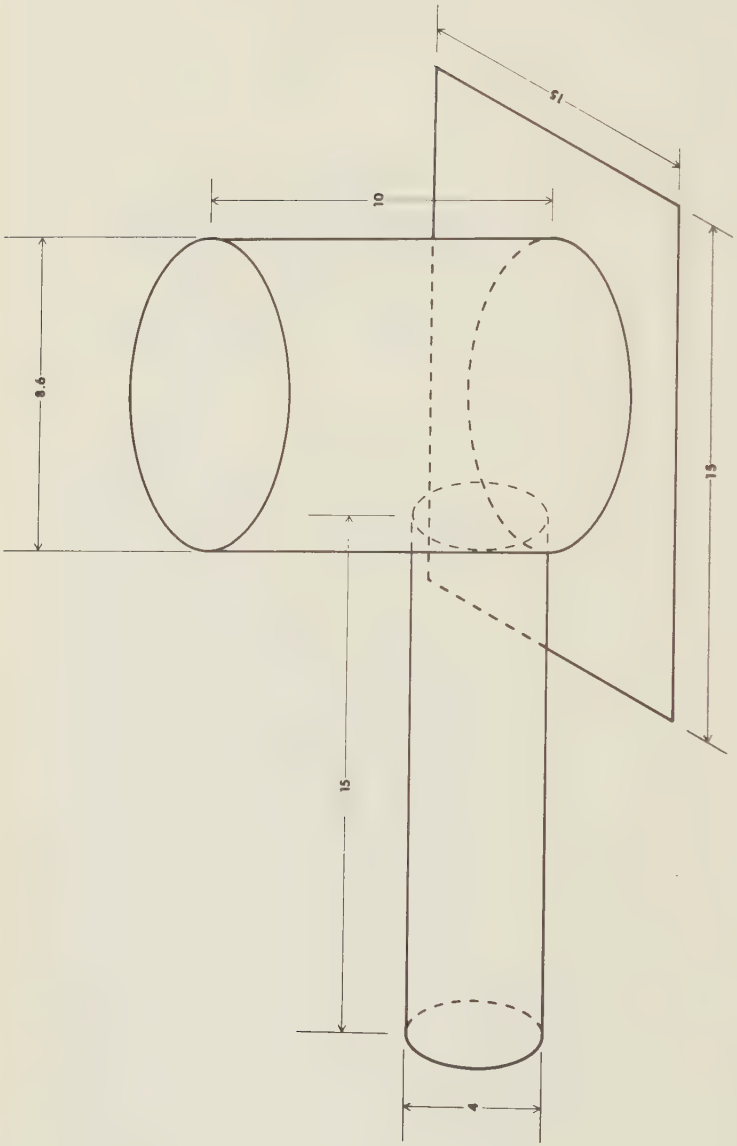

Fig. 4. Paper tape form used to cast epoxy around the coils. Silicone RTV sealer prevents epoxy leakage from the extension while curing. All dimensions are in millimeters.

Electric RTV 102 silicone sealer and tape the lead wires to a flat surface with the open end of the form upwards. Again position the coils parallel to the form and allow 6 hours for the RTV to cure. Check the coil-lead wire continuity.

6. Fill the mold slowly with de-gassed epoxy and allow to cure. Soak the assembly in water and peel off the paper mold. Excess epoxy may then be removed by careful grinding. Form the eyelet from No. 26 copper wire, and attach to the coil with a small amount of Emerson and Cumming Eccobond 26 epoxy. Dip the entire coil in Scotchcast No. 2 epoxy to apply a finishing coat.

CIRCUITRY

Although the secondary coil output may be viewed on an oscilloscope for measurement of the distance between the coils, it is more useful to transform the output amplitude to a DC signal which may be recorded on analog tape or a paper strip chart. The amplifier-demodulator of Figure 5, suitable for this task, also includes a twin-t frequency elimination filter for removal of excitation signal components of a separate set of coils operating in close proximity (5). For single channel operation, the 10 KHz filter may be removed and the secondary coil connected to the 0.1 mfd coupling capacitor via a 100 K resistor. If two-channel capability is desired, another filter-amplifier-demodulator may be constructed with the filter tuned to 20 KHz by changing the 3.3K resistor to 1.5K and adjusting the 5K potentiometer for maximum 20 KHz rejection. The primary coil excitation should be supplied by a stable oscillator capable of developing 30 volts p-p across the 1000 ohm coil impedance, such as the Hewlett-Packard 200 CD.

The above system was designed for simultaneous measurement of left ventricular length and width by two pairs of coils. These measurements have been used to compute ventricular volume continuously by assuming it to be a particular shape (such as a paraboloid of revolution). Other dimensions of interest may also be measured without interference by additional coils operating at different frequencies. However, this addition will require each amplifier-demodulator to be preceded by a series of filters totaling one less than the number of channels. Thus the system becomes somewhat complicated for three or more channels.

A better approach for multichannel measurements is the inclusion of one bandpass filter in each amplifier-demodulator. This improved system, using crystal filters, is shown in Figure 6. Since only a very narrow frequency range is passed by the crystal filter, all of the other excitation signals, regardless of number, are rejected (6). The sharpness of the crystal filter demands a very stable excitation oscillator, so the entire circuit has been

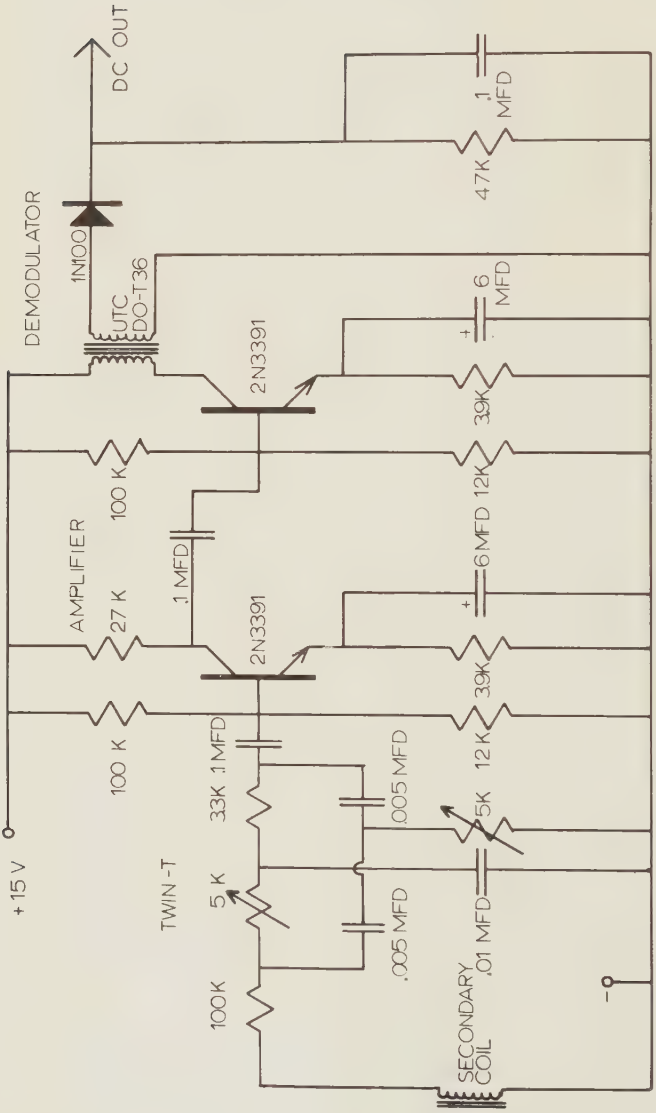

Fig. 5. Amplifier-demodulator for dimension channel operating at 20 KHz. A twin-t filter is incorporated to eliminate interference from a separate 10 KHz channel. Reproduced, by permission, from *Biomedical Sciences Instrumentation*, Plenum Press, 1968.

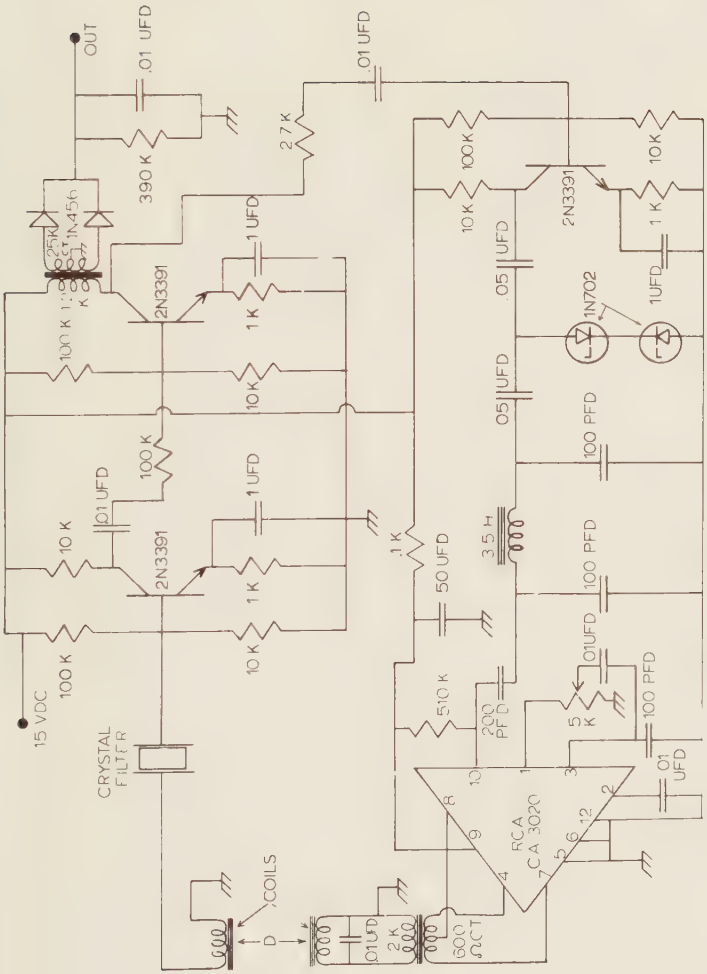

Fig. 6. Schematic of the multichannel self-oscillating bandpass system. The RCA CA3020 primary amplifier is driven by a constant amplitude signal from the overdriven amplifier and clipper-filter. The preceding linear stages supply both demodulator and overdriven amplifier. Reproduced, by permission, from *Medical Research Engineering* 8:4, 1969.

formed into a positive feedback loop to produce oscillation at the crystal frequency. A feedback signal tapped from the amplifier second stage is transformed into a constant amplitude square wave by an overdriven amplifier and zener clipper. It is then reconverted to sinusoidal form by an L-C lowpass filter driving an integrated circuit power amplifier. The transformer coupled output excites the primary coil, completing the loop through the secondary coil. The input to the power amplifier, and thus the 30 volt p-p primary signal, is held constant by the clipper-filter if the coils are within their 10 cm operating range.

This system therefore offers the advantage of self-excitation, but not without the extra concern of coil phasing. If incorrectly phased, negative feedback will result and oscillation will not be possible. This can be corrected by reversing the lead wire to either coil.

The Clevite TSR crystal filters are inexpensive and available in ten frequencies from 10 to 30 KHz. Active operational amplifier bandpass filters may also be designed, and could provide sufficient gain to replace both amplifier stages.

A simpler self-exciting system has been developed for research requiring only one dimension measurement. This circuit (Fig. 7) has a conventional 10 KHz phase shift oscillator driving a complementary symmetry power amplifier for direct coupled primary excitation. The secondary coil signal amplifier is conventional but without the transformer output of the preceding versions. The output operational amplifier, A_2, provides low impedance and an adjustable DC zero control. It may also be used to construct an active output filter for optimum demodulation of fast dimension changes or as a nonlinear amplifier for linearization of the distance-output relationship.

CALIBRATION AND LINEARIZATION

Regardless of the circuit used, a master calibration of each pair of coils should be made before implantation by plotting secondary AC output at 0.25 cm increments between 3 and 9 cm. The primary should be excited by the same frequency and amplitude signal produced by the electronic system. A total system calibration (DC) may also be made if all adjustments are to remain constant, but should be verified by the coil data upon calibration of the recording. This is done by oscilloscope (preferably storage) measurement of the primary coil voltage during two specific events at the measurement extremes, such as systole and diastole of a selected cardiac cycle. These voltages are transformed to displacement by the coil calibration chart and used to calibrate the recording by assuming the coil response to be linear.

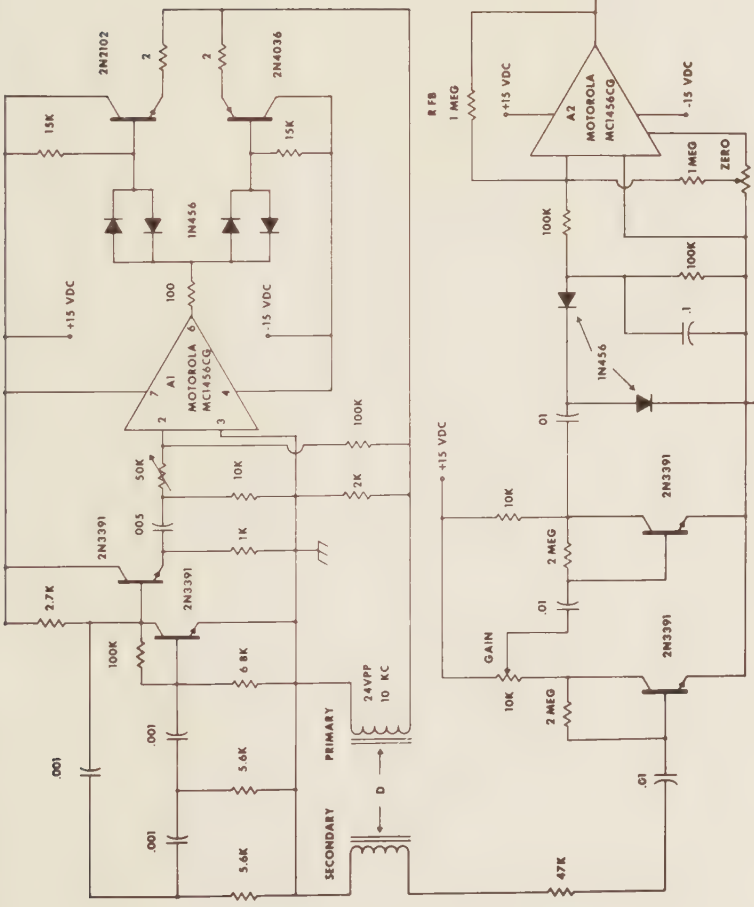

Fig. 7. Single channel system using phase-shift oscillator and operational power amplifier for primary excitation. Secondary amplification is conventional, but A2 nonlinear feedback impedances may be used for partial linearization of output signal.

For small dimension changes, such as the typical 0.5 cm systolic-diastolic width change, the linear assumption does not introduce appreciable error. For measurement of dimension changes that operate over a larger portion of the calibration curve, some degree of system linearization is desirable. For an exact proportional linearization, the inverse cube root of the system output voltage must be computed. This has been performed by modifying the standard analog divider square root circuit to form a cube root circuit, and inverting its output by a separate divider (3). This method should be very exact, but the combined drift and inaccuracy of the inverse cube root circuit causes a large and variable error.

A more practical method is to transform the inverse cube relationship to the simple inverse function of Vout = K/D. This will greatly reduce the error for larger displacements and allow more freedom of choice in methods to compute a reciprocal for complete linearization if so desired. A simple and stable method to perform this cube root extraction is to replace the feedback resistor, RFB, of amplifier A_2, Figure 7, with a General Electric 65D-5010 thyrite varistor. This nonlinear resistor has a current (I) voltage (V) relationship of $I = K_2 V^{2.8}$, where K_2 is a constant. If Vin is the input voltage to this stage, with Rin as the input resistance, and the input current equals the feedback current, then $Vin\ Rin = K_2\ Vout^{2.8}$. Therefore $(\sqrt[2.8]{Vin})(K_3) = Vout$. Since $Vin = K_1/D^3$, the relationship between D and Vout becomes $D = K_4/Vout$. This method is especially valid for $D < 4$ cm, as the exponent of D approximates 2.8 in this range (3).

The above transformation allows the final linearization to be a "simple" reciprocal computation. The most logical way to compute a reciprocal is with an analog divider, and acceptable results may be obtained with one of the more expensive units operating in a stable temperature environment. Another method of computation is an automatic resetting dual integrator circuit which uses the reciprocal relationship existing between the frequency and period of a sawtooth waveform (7). This circuit, although complex, offers much better stability and accuracy than analog dividers.

COIL INSTALLATION AND BIOLOGICAL INTERFERENCE

For measurement of heart dimensions, the coils are attached to the external myocardial surface by sutures through the eyelet and around the epoxy covered lead wire extension. These sutures should be sufficiently tight to minimize coil movement relative to the heart to prevent motion artifacts and misalignment of coil axes. Maximum signal is produced with the coils perfectly aligned, with the output dropping equivalent to a displacement increase of 1 mm for coils 5 cm apart and rotated 30°. The signal

falls very rapidly beyond this point, becoming zero at 90°. The rotation error is complicated by lateral axis misalignments. Both factors are difficult to control due to heart surface irregularities, possible coronary vessel presence in choice coil locations, and changes in heart size and shape during surgery. Coil alignment is also difficult to visualize if both coils cannot be seen simultaneously and if the heart's position is temporarily altered for coil installation. The alignment may be verified before attachment by having the system operative during surgery. This allows the best position of the coils across the desired dimension to be selected by choosing a position in which the output signal is maximal.

Shielded lead wires have been used to reduce capacitive coupling, but are unnecessary if the primary and secondary wires are exteriorized by routes at least 3 cm apart. If two or more dimensions are being recorded by either of the filter systems, the primary and secondary wires may be bunched along two separate routes.

The 520 mg coil produces no noticeable effect on normal cardiac function. Inertial effects of a left ventricular width coil during maximum velocity change are equivalent to a pressure of 0.12 mm Hg, which is small compared to intraventricular pressure. The 20 milliwatts dissipated by the primary coil is assumed to be too small for concern due to the large heat sink provided by the surrounding tissue and fluid. Connective tissue growth, as with any implanted foreign body, surrounds the coils within 15 days and approaches a limiting size that appears to have no ill effects. Although this tissue is generally undesirable, it does hold the coils securely to the heart.

TYPICAL APPLICATIONS

An example of left ventricular diameter measurement is shown in Figure 8. Simultaneous recordings of aortic blood flow and intraventricular pressure are also made to permit phasic comparisons of these parameters during postural changes (8) and exercise (9). A more complete analysis of left ventricular function may be obtained if ventricle length is also measured (10), permitting computation of instantaneous volume. Changes in this volume are compared to the integrated blood flow per cardiac cycle, or stroke volume, to yield a model of the intraventricular cavity.

More accuracy could be obtained in the three-dimensional analysis if errors in measurement due to changes in ventricular wall thickness were eliminated. This has been attempted by insertion of the coils through the wall to measure internal width and wall thickness. This approach has not been very successful due to coil alignment problems and injury to the muscle by the embedded coil extension necessary to hold the coil in place.

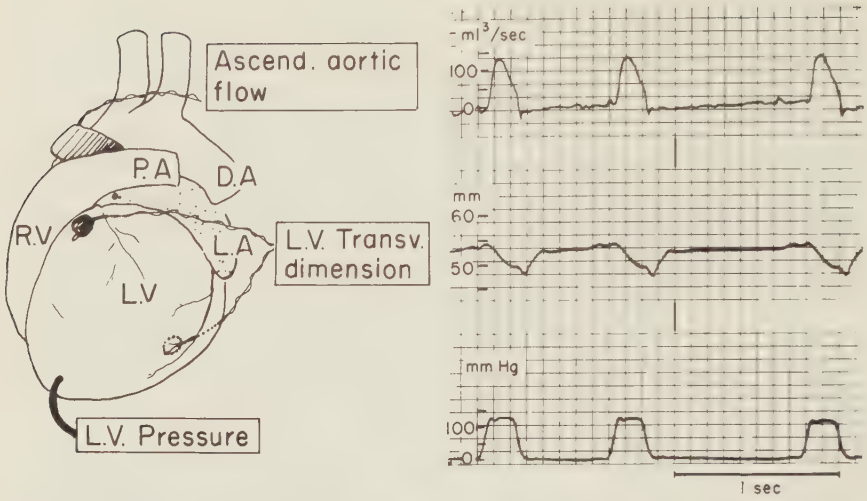

Fig. 8. Location of coils for measurement of left ventricular transverse dimension. Aortic flow and intraventricular pressure waveforms are also provided for phasic comparison. Reproduced, by permission, from *Factors Influencing Myocardial Contractility*, Academic Press, New York, 1967.

However, internal ventricular volume and stroke volume may be easily computed by subtracting a constant from the external ventricular volume. This constant, the ventricular muscle volume, is determined at autopsy by the Archimedes displacement principle. In this way, the geometrical mechanics of ventricular muscle in situ and the cardiac performance of chronically instrumented experimental dogs have been analyzed using relatively simple and inexpensive chronic instrumentation techniques.

SUMMARY

Heart physical dimensions may be accurately measured with two miniature inductance coils which function as a transformer with no mechanical connection between primary and secondary windings. If one coil is supplied with a constant 10 to 30 KHz signal, the voltage induced in the opposing coil will be proportional to the inverse cube of the distance between the coils. Commercially available coils of 1500 turns of No. 48 wire are fitted with a ferrite core and covered with epoxy to form the gauge. These 520 mg coils are sutured to the myocardium for external measurements, but may also be inserted into the ventricle for exact volume computations. The inverse cube root of the secondary voltage can be calculated

if precise linearization is desired, but accurate measurements are obtained by considering the small dynamic operating range of the coils to be linear. If only one dimension measurement is made, the electronic circuitry is simply an audio oscillator, amplifier, and diode demodulator. For multichannel measurements with coil pairs in close proximity, separate excitation frequencies and output bandpass or notch filters must be used to eliminate crosstalk.

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16. A CATHETER-TIP PROBE FOR DYNAMIC CROSS-SECTIONAL AREA MEASUREMENT

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Most of the available methods for the determination of the cross-sectional area of blood vessels in vivo involve computations using measurements of external dimensions of the vessel. These methods make use of strain gages (1, 2), ultrasonic crystals (3, 4, 5, 6,), cinefluorography (7) induction coils (4) and linear variable differential transformers (8, 9). Some of the problems with these methods were the need for surgical implantation of the probe, nonlinear calibrations, and inadequate frequency response. In addition, measurements of linear dimensions and subsequent squaring of quantities leads to almost double the errors in the computed cross-sectional area. Further errors are introduced when internal cross-sectional area is computed from external measurements in the absence of accurate knowledge of the thickness of the wall.

Here, we describe the application to veins of a collapsible mechanical probe and a measuring instrument originally designed by Baan, et. al. (10), to measure dynamic changes in intraluminal cross-sectional area of the aorta. The general principle of the method was developed by Hawthorne (11) to calculate changes in cross-sectional area of the ventricle from external measurements. Our instrument differs from these in that: 1) the mechanical design of the probe allows it to follow the motion of thin-walled vessels, such as veins, with minimal mechanical loading of the wall of the vessel, and 2) the electrical and electronic design makes it possible to obtain high sensitivity and signal-to-noise ratio as well as adequate dynamic response. The instrument described here is suitable for continuous, direct and dynamic measurements of both circular and non-circular cross-sectional areas of intact vessels in living animals. The measuring probe is inserted with minimal surgery and has acceptable loading on the wall of the vessel.

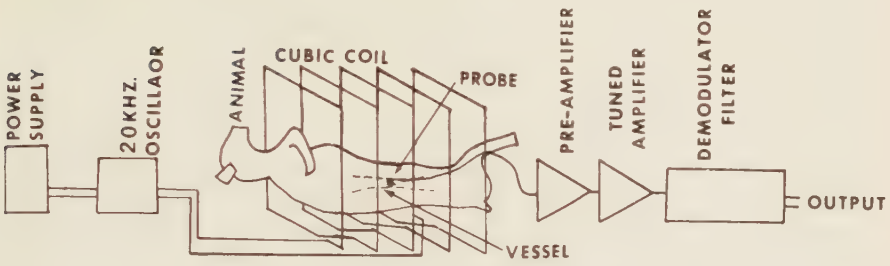
DESIGN PRINCIPLE

The method is based on the installation of a non-magnetic loop within the lumen of blood vessels of live animals. The loop follows faithfully the motion of the cross-sectional contour of the wall of the vessel (12). The animal is placed in a uniform alternating magnetic field axial to the cross-section of the vessel. From Faraday's induction principle, the voltage induced is proportional to the magnetic flux through it, which in turn is proportional to the cross-sectional area of the loop. Since the loop conforms to the cross-section of the vessel, the induced voltage is also directly proportional to the cross-section of the vessel.

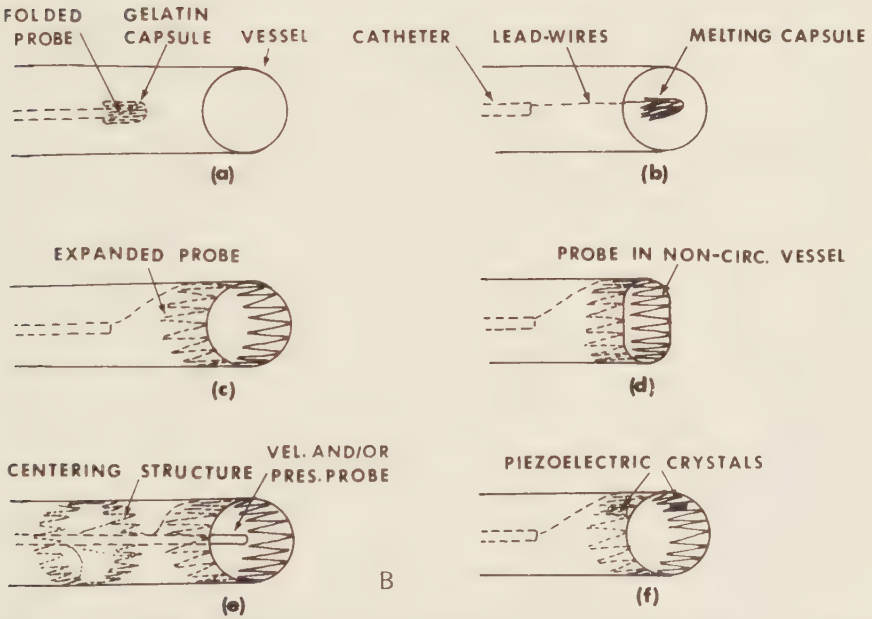
MECHANICAL DESIGN OF THE PROBE

The pickup loop was constructed using a 0.005" diameter beryllium copper wire shaped into a foldable coil (Fig. 1 B). Beryllium copper wire with Teflon coating, available commercially on special order (Sandoz and Co., Culver City, Calif.), could be used to prevent blood clotting. However, we used bare wire and this required heparinization of the animal.

The lead wires from the pickup loop and from another small fixed coil used for calibration purposes were passed through a Teflon tube of sufficient length and 0.05 cm o.d. The fixed coil was wound on the first and the last members of the foldable loop, using several hundred turns of 0.005 mm diameter magnet wire. Total mass of the fixed and the variable coil together was about 20 mg. The pickup loop was folded and placed inside a multilayered, blood-soluble gelatin capsule (made from pharmaceutical capsules), 0.5 cm O.D. and 1.0 cm in length (Fig. 1 B). This assembly was inserted into a 7 Fr. catheter (USCI) and introduced through the femoral vein of an anesthetized dog. The catheter was positioned about 2 cm from a predetermined location of study, in the thoracic or abdominal venae cavae. The tip of the probe was guided to the final place by sliding the Teflon tube enclosing the lead wires, within the catheter (Fig. 1 B). Then, since the probe was supported in the blood stream by a few centimeters of thin Teflon tube, the mechanical loading due to the stiffer catheter was reduced to a minimum. The gelatin capsule melted in about five minutes and the probe sprang open, conforming to the wall of the vessel in the shape of a ring on the internal surface (Fig. 1 B). It followed the motion of the wall of the vessel by spring action.



A



B

Fig. 1. A: Schema of the setup for the measurement of the area of a vessel. B: Schema of a) folded probe inside a gelatin capsule, mounted in a 7 Fr (USCI) catheter and introduced through the femoral vein into the inferior vena cava; b) the probe and the melting capsule are advanced to the location of measurement, the probe now being supported by more flexible lead wires enclosed in a Teflon tube; c) expanded probe conforming to the interior wall of the vessel and following its motion by spring action; d) the probe in a non-circular vessel; e) a foldable structure similar to the area probe is used for centering a velocity and/or a pressure probe in the center of the area probe; f) piezoelectric crystals mounted for the measurement of blood flow using the Doppler principle, along with the area.

DESIGN OF THE MAGNETIC FIELD AND THE ELECTRONIC CIRCUITRY

A uniform alternating magnetic field was generated by using a multiturn cubic coil shown schematically in Figure 1 A. This coil generates a uniform magnetic field (0.01% deviation from the center) in a region 0.45d in length and 0.20d in diameter, where d corresponds to one side of the cube. In comparison, for a pair of Helmholtz coils, this region is 0.15d long and 0.15d in diameter, where d is both the radius and the distance between the pair of coils (13). An added advantage of the large number of turns in the coil is better impedance matching between the cubic coil and the power oscillator feeding the coil.

The voltage induced in the loop is proportional to the product of the frequency and the intensity of the magnetic field (14). For highest sensitivity, both frequency and magnetic field intensity should be made as high as possible. Appropriate design of the power oscillator circuit made it possible to produce a magnetic field intensity of 5 to 10 Gauss within the cubic coil. The frequency was selected so that conventional, low cost, audio electronics components could be used. It was also necessary to obtain adequate frequency separation between other conventional carrier frequencies used, such as 550 Hz for electromagnetic velocity probes, 2 to 3 KHz for pressure transducers, and 5 MHz for ultrasonic measurements. A frequency of 20 KHz was selected based on the above considerations. This high frequency almost completely eliminated the audio frequency noise from the transformers. At this frequency the shunting effect of the blood on the bare probe was negligible.

Since a sufficiently stable commercial excitor oscillator to feed the cubic coil was not readily available, we designed and built one (Fig. 2). It consists of an oscillator built from solid state components, to generate two 20 KHz symmetric square waves (180 degrees out of phase) driving a tuned power amplifier stage (using 2N4297 power transistors). The cubic coil, with a suitable capacitor across it, was pulse excited by the square wave from the power amplifiers and resonated at 20 KHz. This mode of operation causes the output stability of the power oscillator to be essentially the same as that of the power supply feeding the power transistors. The use of a highly stabilized power supply (LH 131A, Lambda Elec. Corp., Melville, Long Island) insured a frequency stability of 0.01% and an amplitude stability of better than 0.1% over a period of two hours under laboratory conditions. Using 15 V for the power stage, the cubic coil was driven at 2 V and 20 A peak-to-peak.

The signals from the variable and the fixed pickup coils were of the

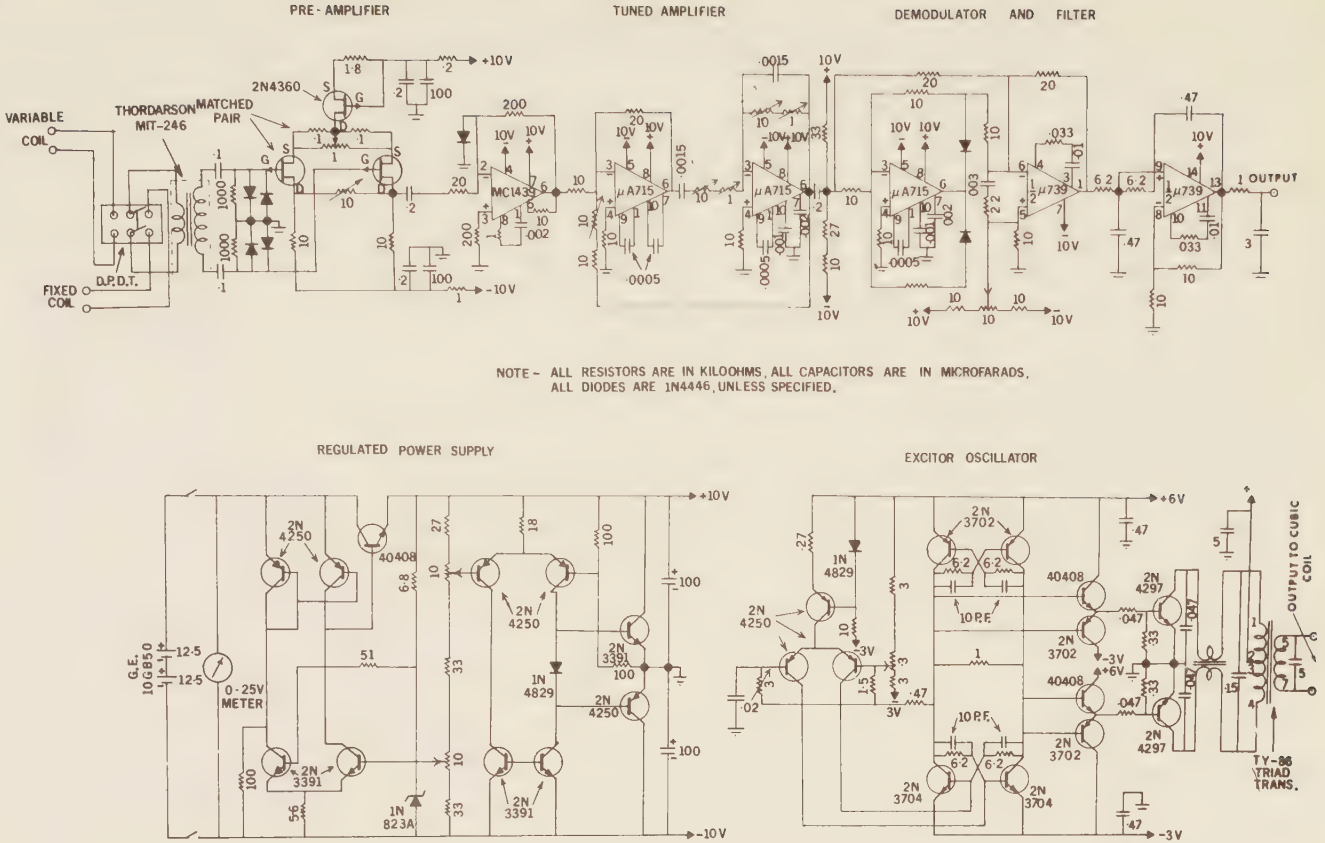


Fig. 2. Schematic of the electronic circuits for the area probe.

order of a few millivolts, modulated over a carrier frequency of 20 KHz, with a bandwidth of approximately 100 Hz. The signal from the fixed coil was used for calibration of the magnetic field. The fixed and the variable coil were connected to the amplifier by means of a double pole, double throw switch. A 2N 4360 matched pair of field effect transistors (FET) was used in the input stage as an impedance matching device (gain 3 db). This reduced the current loading of the probe and subsequently prevented the perturbation of the magnetic field around the loop. The signal from the pickup coil was also stepped up 14 times by using a shielded high frequency transformer. This improved the signal to noise ratio by 30 db. The input impedance of the whole amplifier, including the transformer, was about 10 kilo-ohms (resistive), far higher than that of the pickup coil, which had an impedance of only a few ohms.

The output from the FET stage was further amplified by a Motorola MC 1439 integrated circuit operational amplifier (ICOA) and fed to the tuned amplifier. The tuned amplifier used two high performance Fairchild μ715 ICOAs. The gain of this stage was 60 db, and the bandwidth at a center frequency of 20 KHz was 100 Hz. The output from the tuned amplifier was demodulated by a full-wave detector using Fairchild μ715 ICOAs. The carrier signal was filtered with a third order active filter using one half of a Motorola μ739 ICOA.

The entire receiver was designed to operate on low voltage rechargeable batteries. This minimized the power frequency noise and also the hazard of electrical shock. The battery voltage was further stabilized to give ± 10 V and 0.01% regulation with an open circuit and a full load of 50 ma. This was accomplished by using a special transistor circuit shown in Figure 2. Noise from the power supply was less than 10 micro-volts peak to peak.

The overall signal-to-noise ratio for the electronic circuitry was better than 80 db. The maximum sensitivity was 10 volts per square centimeter of the loop. The frequency response was flat from 0 to 20 Hz and the phase shift was less than 0.5 degrees.

CALIBRATION

The fixed calibration coil has an equivalent cross-sectional area of 2.0 square centimeters. This calibration coil provides an in vivo calibration signal for the calibration of the magnetic field and also facilitates the alignment of the magnetic field with the vessel axis. It is also useful in detecting artifacts due to changes in the orientation of the vessel axis during such activities as breathing. After suitable modification of the external magnetic field, the fixed coil can also be used for detecting the longitudinal motion of the vessel.

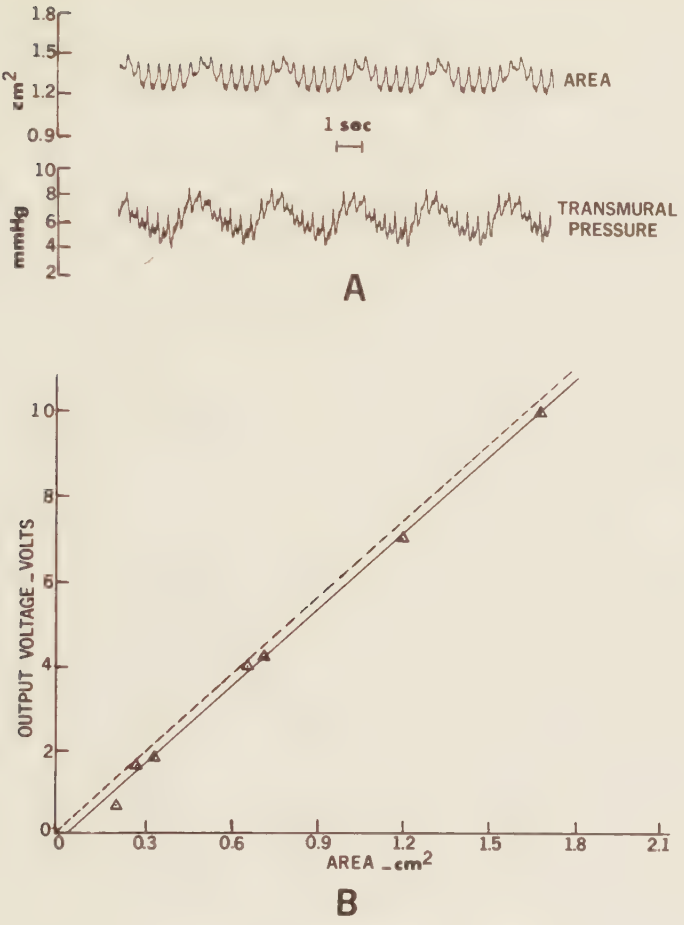


Fig. 3. A: Area and transmural pressure (inside minus outside) in the thoracic inferior vena cava of a dog 1.5 cm distal to the right atrium; pressures were measured using fluid-filled manometers. B: Static calibration of the area probe, where the triangles represent the experimental points and the solid line is the calibration line. The dashed line represents the calibration after correction for the finite thickness of the probe.

For static calibration, a number of plexiglas tubes of precisely known internal cross-sectional areas ranging from 0.2 to 5.0 square centimeters were selected. These tubes were appropriately placed in a uniform magnetic field. The foldable probe was inserted into each of the tubes and the output was recorded. A plot of the voltage and the known area was obtained (Fig. 3 B.). The relationship was found to be linear (solid line), but the line did not pass through the origin. This discrepancy may be attributed to the fact that the probe has a finite thickness of its own and, in addition, it does not fit into the tube perfectly. This effective thickness for the loop can be accounted for by drawing another calibration line through the origin, parallel to the solid line, as shown by the dashed line in Figure 3 B.

MECHANICAL LOADING AND FREQUENCY RESPONSE

The natural frequency of the probe can be calculated from its physical dimensions (14). Similar calculations can be made for the mechanical loading of the wall of the vessel. Both natural frequency and the mechanical loading (subjected to an inverse trade-off or compromise between them) can be adjusted to the desired value, by making appropriate choice of the mechanical properties of the wire and the dimensions of the loop. The theoretical calculations for the mechanical loading were cross checked by obtaining the pressure-volume curves for a segment of blood vessel in vitro, before and after the installation of the probe within the vessel. The difference between these two curves was found to be negligible, reflecting the small mechanical loading of the probe. The natural frequency response in air was checked by mechanically vibrating the probe in the magnetic field and observing the dominant mode of the output signal frequency. Typical natural frequency response for the probes used was 50 Hz in air, and the calculated loading on the wall of the vessel was 0.1 mmHg.

RESULTS AND CONCLUSIONS

Using the electromagnetic probe described above, the changes in the area of the thoracic inferior vena cava of an anesthetized dog were obtained as shown in Figure 3 A. The center of the probe was located about 1.5 cm from the right atrium. The transmural pressure was obtained by subtracting the intrathoracic pressures from the venous pressure measured at the site of the area probe. Both these pressures were measured by fluid-filled manometer systems. The whiplash produced by such a system is evident in the form of small wavelets in the pressure tracing. The subtraction of the two pressure signals was accomplished in an EAI TR-48 general purpose analog computer.

Cardiac and respiratory activites were reflected in corresponding changes in the area of the thoracic inferior vena cava. The cardiac activity became more evident during expiratory pauses.

The transducer can be modified to include a combination velocity and/or pressure probe (Fig. 1 B), to obtain pressure and blood flow rates simultaneously at a given location in an intact animal. A foldable centering structure can be used to support the probe in the center of the area probe (Fig. 1 B).

We have not tried the area probe in unanesthetized animals, but the method can be suitably modified for use in chronic implantations. For example, Teflon coating would eliminate the need for heparinization. The external magnetic coil can be modified to fit in a flexible harness around the rib cage of the animal. Alternately, the magnetic field can be provided by an internal coil. However, in this case the magnetic field is nonuniform and this, in turn, introduces non-linearities in the calibration.

SUMMARY

This paper describes the design and construction of an instrument suitable for continuous, direct and dynamic measurement of both circular and non-circular cross-sectional areas of intact vessels in living animals. A foldable non-magnetic loop, constructed with thin beryllium copper wire, was inserted through the femoral vein to the central vein of a dog. The loop was held in a blood-soluble gelatin capsule and mounted in a 7 Fr. catheter. The gelatin capsule melted in a few minutes and the loop conformed to the wall of the vessel and followed its motion by spring action. The dog was moved into a uniform alternating magnetic field and the voltage induced in the loop was suitably amplified. From Faraday's induction principle, the voltage induced in the loop is proportional to the magnetic flux through it, which in turn is proportional to the cross-sectional area of the loop and the internal cross-sectional area of the vessel. The probe was found to have excellent linearity, adequate dynamic response and acceptable loading on the wall of the vessel.

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17. COMPARISON OF FOUR DIMENSION TRANSDUCERS

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Over the past 15 years, beginning with a year in the laboratories of Robert Rushmer, we have used dimension transducers on a variety of organs: liver, spleen, kidney, portal vein, vena cava, pulmonary vein, and the heart. We have utilized three techniques which are relatively simple, but which are not easily quantifiable. Thick-walled rubber tubing with a small external diameter (approximately 2 mm) was filled with mercury, and connections with plastic coated wires were made at each end (1). The fine rubber tubing was drawn through the capsule of the liver or spleen and anchored at each end with a Teflon disk. As the dimensions of the organ increased, the column of mercury was lengthened and its cross-sectional area was reduced, resulting in an increase in resistance. The mercury-in-rubber gauge was used as one arm of a bridge; no attempt was made for temperature compensation since the gauges were used internally where a constant ambient temperature was provided by the animal. Although linear for the strains in our studies, this "Whitney gauge" method was too fragile for chronic experiments and unquantifiable. The technique is most useful in non-invasive studies of human or animal limbs, particularly in those studies requiring direct exposure of the limb to ambient conditions (2). With external applications, calibration is possible by the simultaneous use of conventional plethysmographic techniques, or by the use of micrometers to introduce known increments of strain. Extraordinary sensitivity for the technique can be achieved by the use of transformer coupling.

Total impedance across an organ was measured using the 2400 Hz source of a Sanborn carrier amplifier (1). Silver-coated electrodes were sewn to the capsule of the liver or spleen. The method allowed very high-gain recordings, and the only system failures were due to the animal chewing off the external wires. However, quantification was difficult in the liver and spleen studies because of the highly variable cell content of the blood in the spleen with contraction (3).

Miniature mutual inductance coils have been very reliable for recording changes in dimensions of organs with a wide range of sizes, ranging from the liver and spleen to pulmonary veins. In the larger organs, we used 400 turns of 1-mil, enamel-covered copper wire with a 15 mm diameter. The air core coils weighed 160 mg. The primary coil was connected to the 2400 Hz oscillator of a Sanborn carrier amplifier; the voltage induced in the secondary coil was amplified, after demodulation, and recorded with the polarity arranged so that an upward galvanometer deflection represented an increase in size. The relationship between the voltage induced and the separation of the coils is an inverse one, which is roughly linear for small strains. Records with mutual inductance are indistinguishable from those obtained with a modified sonar method, which is quantifiable and linear (Fig. 1). For the

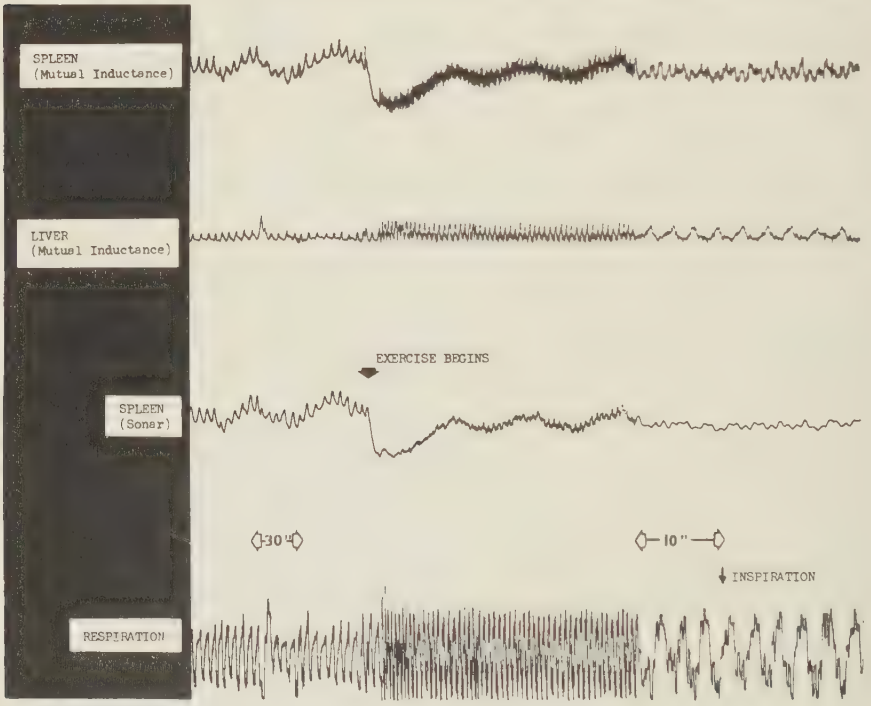

Fig. 1. Dimension recordings from a dog running on a treadmill. The spleen diameter is recorded by two methods, mutual inductance coils and ultrasonic transit time. There is no appreciable difference in the analog records with the two techniques, although no attempt was made to compensate for the non-linear characteristics of the mutual inductance method. Reproduced, by permission, from the *American Journal of Physiology* 204:35, 1963.

study of veins we have used smaller coils, weighing 80 mg, consisting of 200 turns of wire, 6-7 mm diameter, and a 100 kHz oscillator. The only major disadvantage of the mutual inductance method is the difficulty of calibration in vivo in chronic animal experiments, and in the non-linear voltage/displacement relationship for greater displacements.

Pulsed ultrasound transit time is the only method we have used which permits the precise determination of the dimension of an organ at any time. We originally used 3 MHz excitation of 5 mm disks of barium titanate with acoustical backing. We modified the original instrument of Rushmer, et al (4) to permit studies at separations of 5 mm or less (5). Ease of calibration and reliability are the ultimate advantages of the ultrasonic transit time instrument. The interval between the excitation pulse and the leading edge of the receiver pulse may be determined from a good quality oscilloscope; the interval in microseconds multiplied by 1.5 indicates the separation of the two piezoelectric crystals in millimeters for blood and lean tissue. (The transit time for fatty tissue is sufficiently different to permit monitoring of changes of blood volume in a segment of mesentery) (6). The transit time technique for distance is linear, and permits calibration of the overall dimension, as well as the pulsatile changes, at any time during a prolonged chronic experiment. The changes produced by intervention can be expressed most simply in terms of a percentage of the resting dimension, or converted into volume changes at the end of an experiment by infusions of known quantities of blood (1).

The advantages of both quantification and stable recordings can be achieved by combining the ultrasonic and mutual inductance transducers with the mutual inductance coils on the perimeter of the piezoelectric crystal. This was particularly important at an earlier stage of development of the ultrasonic instrumentation when the ultrasonic beam was excessively narrow, and near-perfect alignment of the two crystals was required to assure a stable analog record of dimension.

Improvements of ultrasonic design to achieve a wider beam began with convex acoustical lenses added to the front of the crystal. These lenses have a damping effect on the crystal, and increase the power requirement. Much greater efficiency may be accomplished through the use of crystals cut from a spherical or cylindrical cast. Unfortunately, small-radius spheres have not been commercially available. Our solution is the use of small flat crystals of lead zirconate-titanate at 3 MHz, with a convex lens of acrylic, and refinement of the electronics to produce an extremely short excitation pulse, less than 0.5 microseconds. This has permitted the use of a single transmitter crystal (without acoustical backing) on the endocardial surface of the left ventricle, and receiver crystals on the opposite ventricular wall for diameter

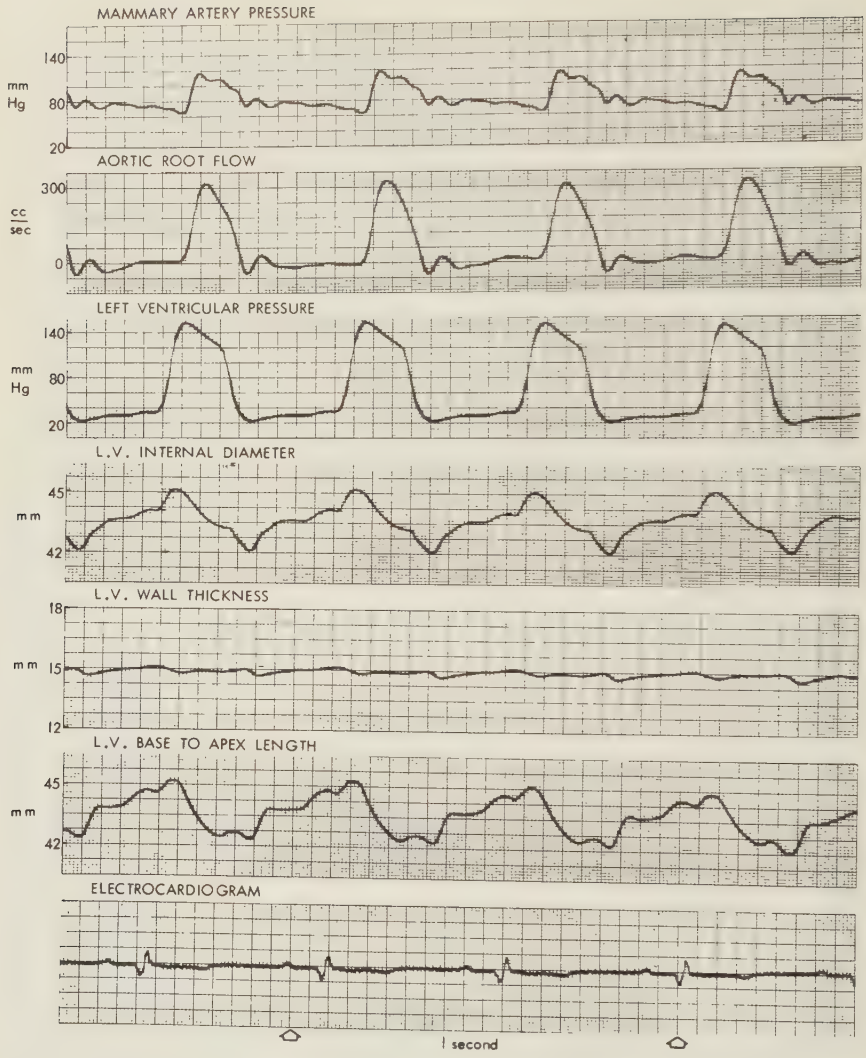

Fig. 2. Recording in a chronic animal preparation illustrating the capability of a modified ultrasonic transit time instrument. A single piezoelectric crystal of lead zirconate-titanate on the endocardium of the left ventricle (L. V.) is the transmitter. Additional crystals receive the 3 MHz signal at the opposite endocardial surface (L. V. internal diameter), adjacent epicardial surface (L. V. wall thickness), and endocardial surface at the apex (base to apex length).

changes, on the epicardium immediately adjacent for wall thickness, and the apex of the ventricle for inflow length changes (Fig. 2) (7).

SUMMARY

Mercury in rubber tubing provides a variable resistance gauge which we have used in chronic animal studies of liver and spleen dimensions. The gauges proved to be excessively fragile for chronic implantation, but were ideal for non-invasive studies of limb volume changes with exposure to variable ambient temperatures. Total impedance changes across an internal organ were easy to record, using a two electrode technique, but quantification was difficult, particularly when the hematocrit varied as it does with splenic contraction in the dog. Miniature mutual inductance coils have virtues of ease and reliability of recording a wide range of dimensions, but disadvantages of non-linearity and difficulty of calibration in chronic animal experiments. We regard pulsed ultrasound transit time as the method of choice for displacement recording. The output/displacement relationship is linear, and calibration is possible at any time during an extended period of study. The major instrumental problem has been excessive directionality of the ultrasonic beam. Improvements in broadening the effective spatial angle of the beam have been achieved with spherically or cylindrically cast crystals of lead zirconate-titanate, and through electronic improvements by extreme shortening of the excitation pulse.

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18. MINIATURE IMPLANTABLE ACCELEROMETERS

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Few studies have been reported in the literature on the use of accelerometers for studying physiologic phenomena. In each case these transducers have been placed on the body surface to study vibrational characteristics of the chest wall (1, 2) or to obtain ballistocardiograms. More recently, the ability to detect acceleration from biologic structures has resulted in the detection of heart rates of chicken embryos and roaches and the activity of heart cells in culture (3). The use of such devices for direct study of organ position and motion has been hampered by transducer size and the lack of adequate means for obtaining acceleration information from appropriately instrumented animals, whether anesthetized or in an awake state. It is the purpose of this report to present preliminary results describing the use of miniature single and three axis accelerometers, capable of long term implantation within the body, which have been used to obtain information about the functional state of the left ventricle.

METHODS

Commercially available single- and three-axis accelerometers (supplied originally by Electro Optical Systems, Inc. Pasadena, California, and more recently by Konigsberg Instruments Inc., Pasadena, California) were utilized in these studies. A single-axis transducer is schematically illustrated in Figure 1. Acceleration is detected by the strain developed in a cantilever beam due to the deflection of a seismic mass. A platinum weight is used for the mass, a platinum beam is used for the restoring spring, and solid state silicon gauges sense strain or deflection of the beam. Change in resistance of the strain gauges which are placed on each side of the deflected beam is proportional to acceleration, since $F = ma$. Output is sensed by a half Wheatstone bridge which provides roughly 2 mv/g with 5V excitation. Accelerometers of this type have resolution accuracies to less than 0.01 g up

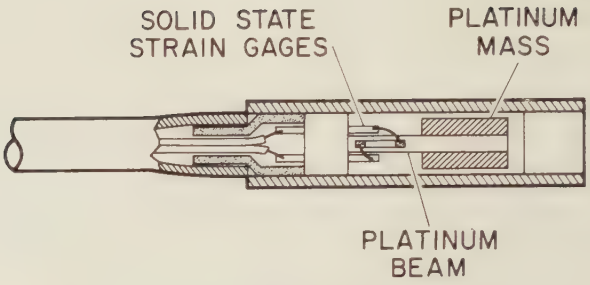

Fig. 1. Cross-section of single-axis accelerometer.

to 100 g. The unit has a resonant frequency of approximately 500 Hz, but this can be raised if needed at the expense of sensitivity to acceleration. The units are made in single-axis form and bonded at 90° angles to form dual- or tri-axis units. The single axis accelerometers measure 0.2 x 0.5 x 0.6 cm; the three axis accelerometers measure 0.9 x 0.6 x 0.6 cm. Each device is hermetically sealed within a stainless steel or titanium container to prevent intrusion of body fluids when chronically implanted inside the body. A half Wheatstone bridge configuration has been used throughout, although such units have only one-half the output of a full bridge. The half bridge units have the convenience of fewer internal leads (3 lead wires vs four or five leads), have proven more reliable, and are more convenient when used in hard wire or particularly for telemetry applications. A silicone oil is used for internal damping. The units are additionally compensated for temperature changes.

Single- or three-axis transducers have been attached to the anterior and/or posterior surfaces of the left ventricle at the time of left lateral thoracotomy in all cases. Figure 2 illustrates a left lateral radiograph of a chimpanzee with a three-axis accelerometer implanted on the posterior surface of the left ventricle. Signals were obtained from such implanted transducers by a telemetry link as shown in Figure 3. The transducers were attached to the external left ventricular surfaces by sutures placed through the eyelets of the sealing case shown in this figure. Figure 4 is a photograph of a typical eight channel implanted telemetry unit as used in this study. Both five and eight channel telemetry systems were utilized for these purposes. The operation of such multichannel telemetry units has been described previously (4) and is discussed elsewhere in this volume. Each transducer was carefully calibrated on a shake table before use; a typical calibration record is shown in Figure 5. All readings of output voltage are in volts.

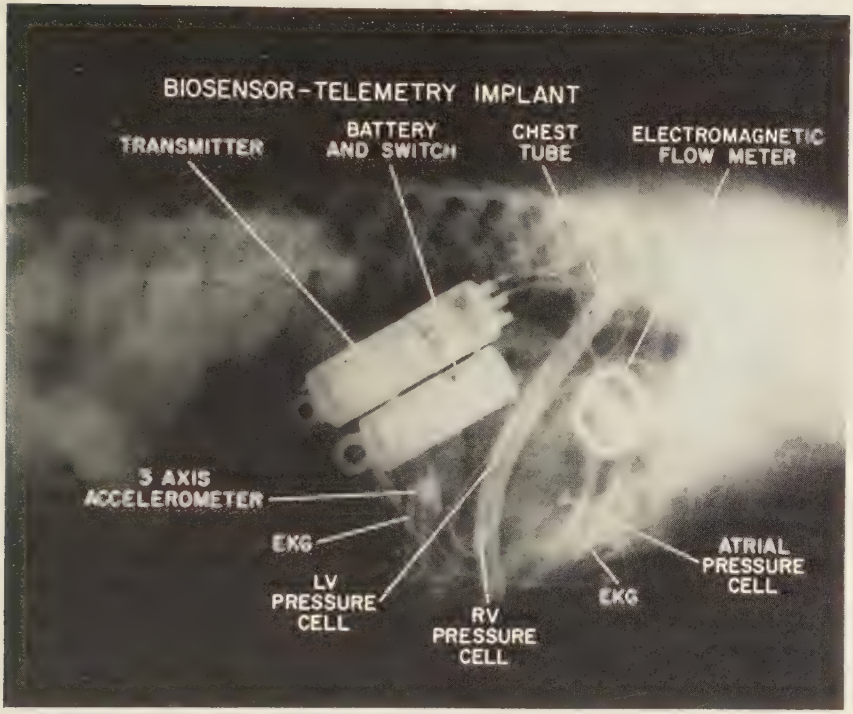

Fig. 2. Lateral chest x-ray of chimpanzee.

The method for obtaining dimensional change from the accelerometer traces has been reported previously (5). These methods are based on doubly integrating the acceleration trace. Data utilized for such purposes was obtained from acceleration traces recorded on an Ampex FR 1800 tape recorder at 1½ ips. Initially dimensional changes were obtained by analog means (5); more recently they have been obtained by A-D conversion of these traces and double integration using Fortran programming and an IBM 360/67 computer.

RESULTS

Accelerometer implantations have been accomplished in eleven dogs and 6 chimpanzees to date. A typical tracing obtained from the use of two three-axis accelerometers in a dog one week post-operatively is illustrated in Figure 6. A radio-telemetry link was used as shown in Figure 3. Quantitative displacements of the anterior and posterior walls as obtained by these methods are also shown in this figure. Acceleration data obtained from

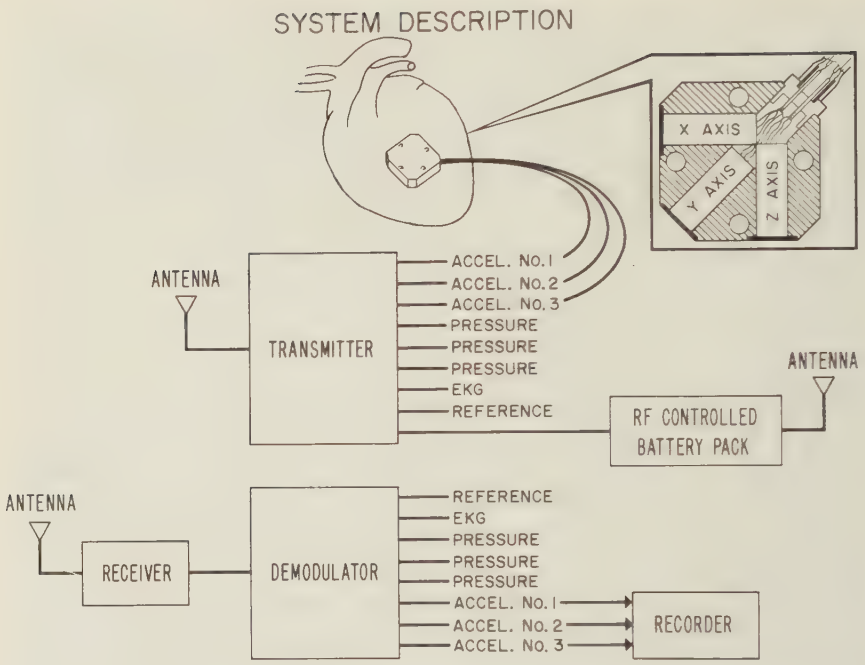

Fig. 3. Schematic of telemetry system for obtaining accelerometer tracings.

various awake animals showed little difference in form, compared favorably with those previously reported in the literature, and resembled a phonocardiogram (1, 2). Changes in magnitude of the acceleration and displacement traces occurred with various interventions. Using a three-axis accelerometer, a characterization of spatial motion of the ventricular wall can be obtained. Figure 7 compares the displacement tracings for the anterior and posterior walls shown in Figure 6. The anterior wall is shown to have an onset of contraction which is slightly earlier than the posterior wall in the head-to-foot (x) direction. The magnitude of change in the front-to-back (z) direction is greatest for posterior heart wall motion. There is a slight but definite torque (y direction) during contraction. These spatial motions have occurred for all dogs analyzed to date. Figure 8 demonstrates a typical single axis accelerometer tracing obtained by telemetry in a chimpanzee following surgery. Vibrational movement of the anterior wall slightly exceeded posterior wall movement immediately post surgery. Changes occurred on the first day after surgery so that the acceleration traces were nearly equal; by the second day after surgery, posterior wall motion exceeded anterior wall motion and remained so for the duration of each study. Findings such as these have also occurred for all animals studied to date.

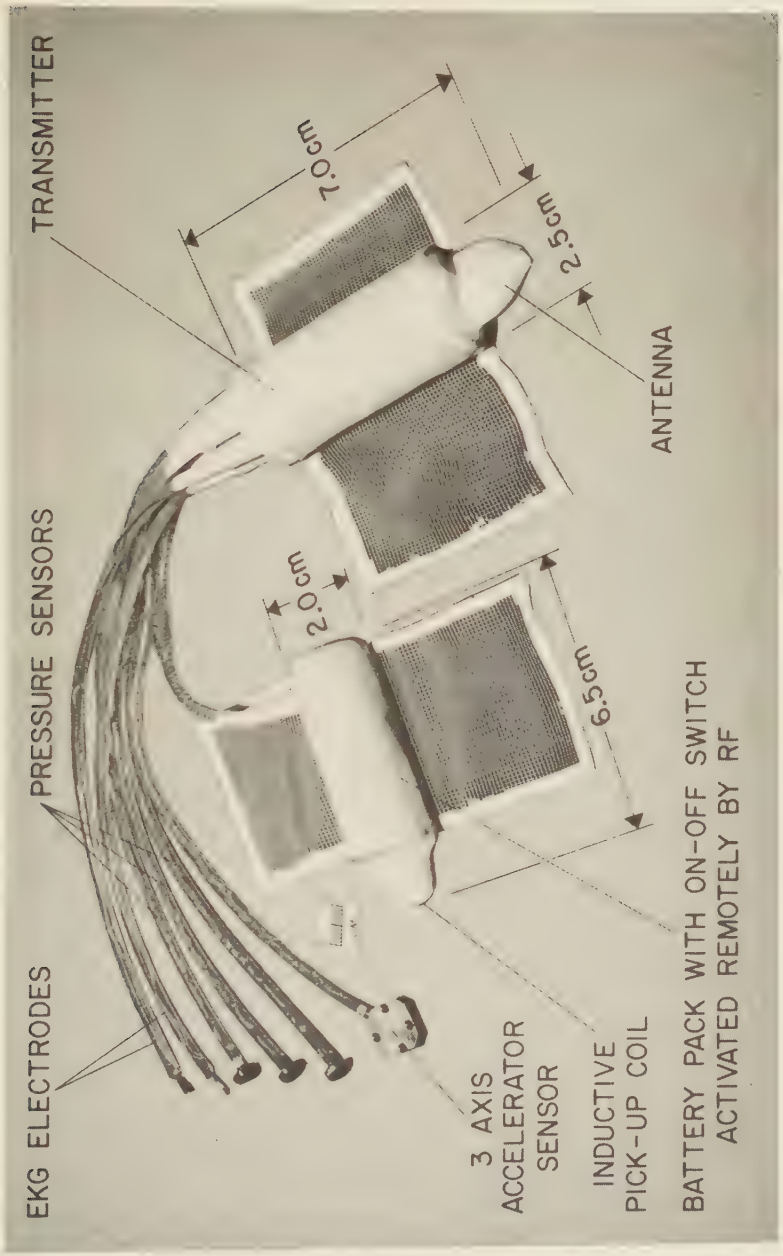

Fig. 4. Multichannel telemetry transmitter.

TRANSDUCER BA-3, SER No.11 (VOLTAGE AT DEMODULATOR OUTPUT)

		1g	2g	3g
CH. 2	+X	+0.410	+0.82	+1.23
	-X	- .396	- .72	-1.19
CH. 3	+Y	+ .245	+ .550	+0.83
	-Y	- .273	- .550	-0.83
CH. 4	+Z	+ .433	+ .866	+1.50
	-Z	- .442	- .884	-1.33

TRANSDUCER BA-3, SER No. 12

CH. 5	+Y	+0.402	+0.804	+1.21
	-Y	- .388	- .776	-1.16
CH. 6	+X	+ .488	+ .866	+1.30
	-X	- .420	- .840	-1.26
CH. 7	+Z	+ .472	+ .944	+1.42
	-Z	- .460	- .920	-1.38

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POSITIONS OF TRI-AXIS ACCELEROMETER WITH RESPECT TO EARTH FOR 1g INCREMENTS CONSISTENT WITH THE FRAME OF REFERENCE SHOWN PREVIOUSLY. (VERTICAL IS NULL POSITION)

Fig. 5. Calibration of tri-axis accelerometers.

DISCUSSION

Dimensional changes for the left ventricle can be obtained by other less expensive methods such as mercury-in-rubber strain gages, ultrasonic crystals, and mutual inductance gages (6, 7, 8). A characteristic of such systems is that they provide an integrated measure of ventricular dimensional change in the plane of the transducer and are difficult to use for studies of heart geometry requiring information concerning absolute or differential movement of the respective chamber walls. Several specific methods are available for such purposes and consist of insertion of lead beads (9) or tantalum screws (10) into vascular, atrial, or ventricular walls. These latter methods require the use of expensive x-ray equipment and complicated data reduction schemes which are far more expensive and time consuming than the presently used accelerometers. Accelerometers, at present, provide the only means of studying isolated wall motion in an awake, unanesthetized animal without the use of continuous-recording x-ray equipment.

It must be realized that the length changes resulting from analysis of accelerometer tracings represent relative, rather than absolute, changes in dimensions. Each trace must be calibrated by an independent means for determining end-diastolic size in order to make absolute measurements.

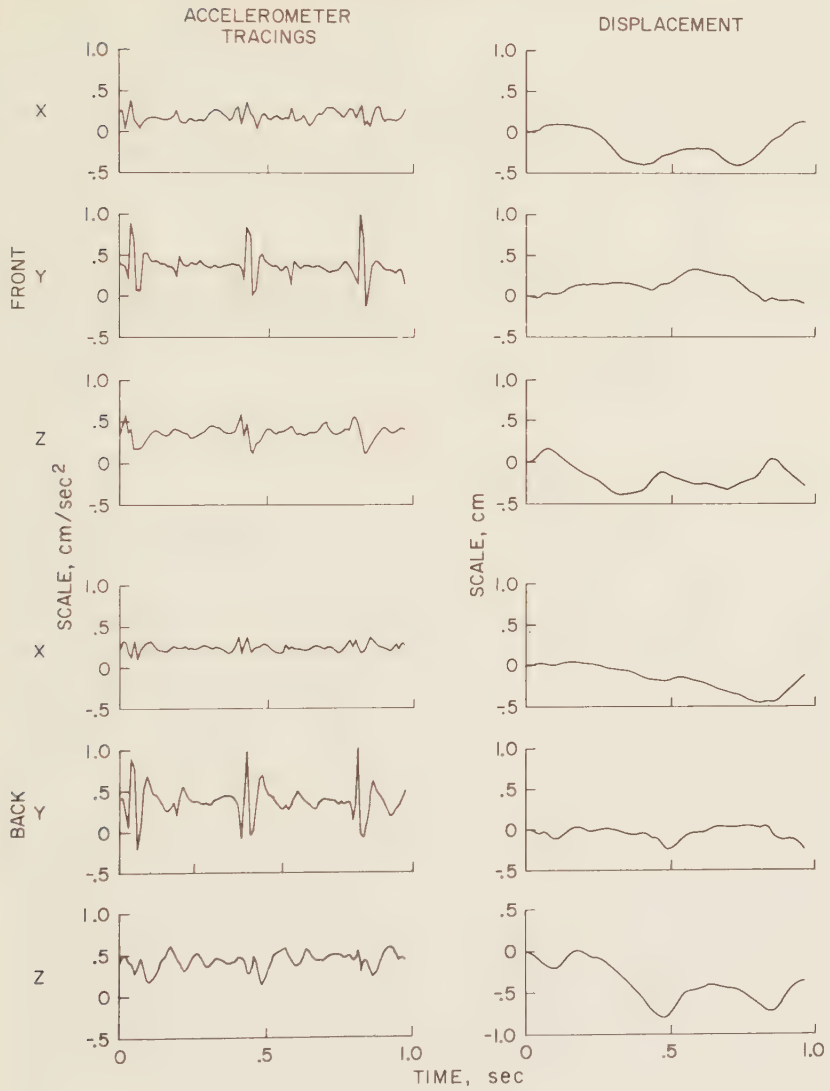

Fig. 6. Accelerometer and displacement tracings in a dog.

Absolute calibration of size has usually been accomplished by angiocardiography in this laboratory; other x-ray or instrumentation techniques as described above can also be used. Experiments are presently in progress to use a single timed chest radiograph for these purposes in order to extend the capability of these transducers to make quantitative rather than qualita-

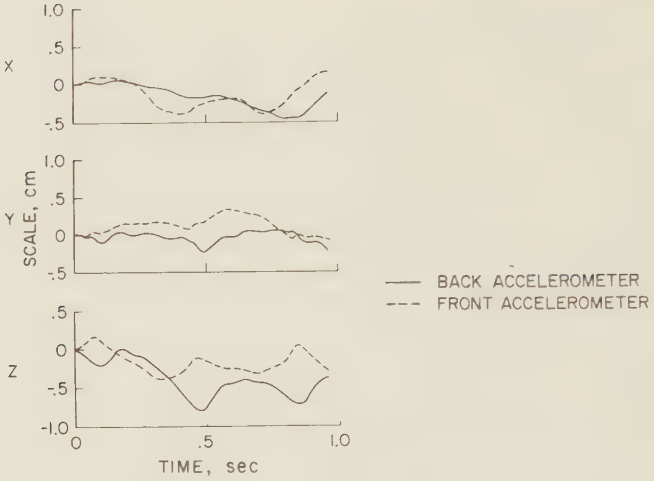

Fig. 7. Comparison of displacements from front and back accelerometers.

tive measurements. Recently, the need for accurate study of isolated heart wall motion has become apparent as left ventricular function studies are being conducted in animals with experimental myocardial infarction. Various and multiple areas of the heart wall are being followed subsequent to infarction to determine the effects and consequences of such lesions. The use of implanted accelerometers would appear to have a place in such an evaluation, using measurements of the type shown in Figure 7.

The ability to follow and determine the vibrational characteristics of the heart from implanted gauges has other potential research applications. Chief among these is the ability to correlate heart sound production and the elastic properties of the heart wall. It has been known for a considerable period that heart sounds change in the presence of myocardial infarction (11). Additionally, it has been shown that acceleration of blood flow is associated with sound production in the cardiovascular system (12). Recently, it has also been shown on theoretical grounds that the elastic properties of the heart are involved with sound production (13). The ability to measure directly left ventricular heart wall vibrations with simultaneously determined heart sounds, pressure, size and shape will provide invaluable information about the elastic properties of the heart, particularly the left ventricle. The proposed results of such studies, which are presently in progress, will be determination of the material properties of the heart wall from an intracavitary, manometer-tipped catheter providing simultaneous heart sounds and pressure recordings.

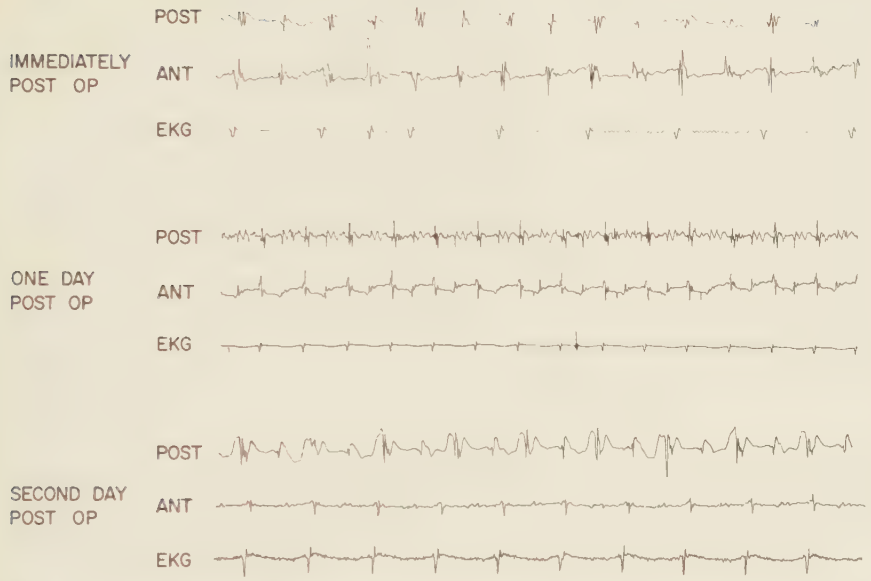

Fig. 8. Comparison of single axis accelerometer tracings for three consecutive days in a chimpanzee.

SUMMARY

Preliminary results have been presented using a miniature implantable accelerometer system which allows for the recording of the vibrational characteristics of the left ventricular wall in chronic animal preparations. Early studies with this system demonstrate its usefulness in determining the relative dynamic geometry for isolated segments of the ventricular wall which cannot be obtained easily by other means. Such methods have immediate use in the study of experimental myocardial infarction. Accelerometry methods show future promise in correlating heart wall material properties with sound generation in the cardiovascular system.

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19. ELECTROCHEMICAL CRITERIA FOR SELECTION OF CHRONICALLY IMPLANTED STIMULATING ELECTRODES

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INTRODUCTION

If a constant-current pacemaker impulse (square wave) is applied to body tissue through a pair of physiological electrodes, the resulting voltage waveform is not square, but rather it rises exponentially. In engineering terms then, the load seen by the pacemaker is not wholly resistive, but rather is capacitive in nature.

Early investigators (1) attributed this capacitive nature to the known capacitive characteristic of nerve membrane. However, Schwan et al (2) recognized it as electrochemical polarization. Greatbatch (3) demonstrated the effect in vitro in saline with no tissue at all, and Mansfield (4) proved the effect to take place entirely within one micron of the surface of the metal electrode.

Electrochemical polarization of physiological electrodes is an important aspect of electrode selection. Electrochemical data give considerable insight into the reasons for electrode degradation, the service life expectancy of any given electrode system, and the efficiency of coupling the pacemaker impulses to body tissue.

Electrical current in metals is a flow of electrons. Electrical current flow in body tissue, however, is a flow of ions, that is, of charged atoms or molecules that have either a deficiency or an excess of electrons in their outer rings. In order to transfer the energy of a pacemaker impulse from the electrode wire to body tissue, electron flow in the wire must be converted to ionic flow in the tissue. A chemical reaction is necessary at each electrode to accomplish this. The chemical reaction at the positive electrode (anode) will necessarily be completely different from that at the negative electrode (cathode).

The identification and quantification of these reactions is the target of several extensive research efforts today, one of these being at Houghton

College, Houghton, New York (5). To date we have identified four distinct classes of electrode metals, differentiated by the chemistry of their coupling reactions. Two of these, silver and the stainless steels, feed on their anodes and can destroy their electrodes in a corrosion process. Another, platinum, operates nearly solely on a catalytic modulation of the level of adsorbed monatomic oxygen. The fourth, titanium, has properties recently discovered by us and first reported here. Titanium provides a large capacitive coupling through some process on the metal surface which is neither catalytic nor involves a corrosion process. We have not yet completely identified the process.

POLARIZATION MEASUREMENTS

We have studied electrode metals by applying a chain of galvanostatic (constant-current) impulses to an electrode pair, each 0.010" in diameter and 2 cm long (0.16 cm^2 area). This chain consists of nine sequential impulses, 2 ms in duration and 1, 2, 3, 4, 5, 6, 7, 8, and 9 ma in amplitude. The resulting voltage developed across the electrode interface is measured by a 3 electrode technique and displayed in the form shown in Figures 1 to 5. The medium is physiological saline at 37°C. Earlier work (3) showed that results obtained in 37°C physiological saline were, for all practical purposes, identical to those obtained in vivo if allowances were made for the diluting effect of the lower conductivity of tissue and particulate matter in the body electrolyte.

NOBLE METALS

Platinum. As seen in Figure 1, platinum metals exhibit nearly identical polarization voltages on anode and cathode. This is surprising, since one expects different reactions on anode and cathode. Our studies have now convinced us that electricity couples into the body through platinum electrodes by a modulation of the level of catalytically adsorbed oxygen on the surface of each electrode (5). The reactions on both anode and cathode are reversible and are:

$$H_2O \leftrightharpoons O_{ad} + 2H^+ + 2e^- \qquad (1)$$

This reversibility explains the identical nature of anodic and cathodic waveforms. The catalytic nature of platinum explains the surprisingly large energy capacity of the platinum surface, some 1100 microcoulombs per cm^2. One monolayer stores enough electricity for some dozens of pacemaker impulses, even without replenishment of the surface. Lightly alloying

platinum (up to 10%) may greatly increase its strength without significantly affecting its electrical performance. Iridium is usually used as the second metal.

We have also considered gold and its alloys (3) but have never used them clinically. High-strength gold alloys contain significant proportions of base metals. Although our concern about the effects of these contaminants is purely theoretical, we have preferred to use high-strength platinum with 10% iridium for clinical applications.

Thus, platinum metals are probably electrically ideal for physiological electrodes. They couple well and are absolutely inert in the body. However, they are costly and are not as strong as some other electrode metals. We have used platinum metals nearly exclusively for chronic clinical physiological electrodes.

SILVER METALS

Figure 2 shows silver as being characterized by a polarizable anode and a non-polarizable cathode. No appreciable post-pulse charge is seen on the anode. The reason is that pulsing a silver electrode anodically causes the silver to react with the chlorine ions in solution to form a silver chloride surface. Pulsing cathodically strips the electrode and leaves bare silver, a highly polarizable surface. The electrical coupling is very efficient in this exchange but the silver anode is consumed in the process. Also, the toxicity of silver ions in the body is still being argued.

NON-NOBLE METALS

In this class we have included all the stainless steels, elgiloy, and cobalt alloys such as imploy, etc. We have excluded titanium, which will be discussed later.

The non-noble metals are characterized by quite high threshold voltages. As seen in Figure 3, generally 0.6 V or more is required to pass a 1 ma pulse. Anode voltages are generally higher than cathode voltages and, as seen on the elgiloy anode in Figure 3, may present some very aberrant patterns.

The aberrant anodal patterns suggest corrosion reactions and indeed, we have identified iron, cobalt and chromium ions in solutions in which these metals had been anodically pulsed for some thousands of hours.

When a blocking capacitor is placed in series with the electrode, such corrosion residues are found coming from both anodes and cathodes if a protective diode is not used (cathodal protection). The reason for this is

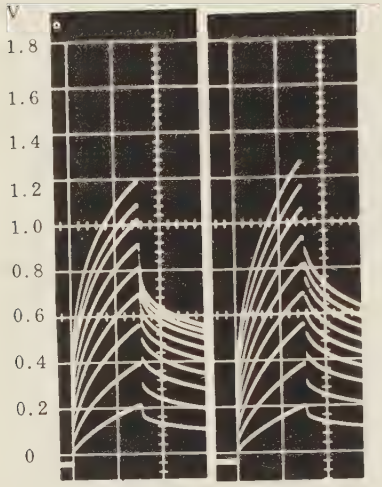

Fig. 1. Platinum electrodes, left-anode, right-cathode, horizontal scale intervals are 1 ms.

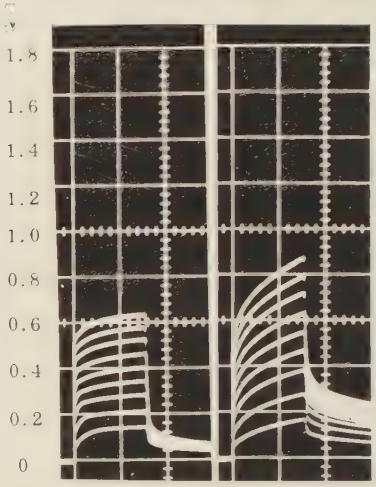

Fig. 2. Silver electrodes, left-anode, right-cathode, horizontal scale intervals are 1 ms.

that a high-quality blocking capacitor assures a zero net electron flow through the electrodes. If average current is zero and a large negative current flows during the 2 ms impulse, then a very small positive current must flow for the 998 ms between pulses. This constitutes corrosion current, even on an electrode nominally considered to be a cathode.

From the above considerations, we can conclude that non-noble metals should not be used for the anode of a small-geometry electrode pair. If a non-noble metal is used as an anode, it should be of very large area, as a side plate or a case of a pacemaker. That is to say, current density should be low.

If non-noble metal is used as a capacitor-coupled cathode, diode protection must be provided. Care must be used to avoid mating a replacement pacemaker without diode protection (perfectly safe for platinum electrodes) to a non-noble electrode. Most contemporary pacemakers have this diode protection, but most pacemakers made in the first half of the last decade did not (6).

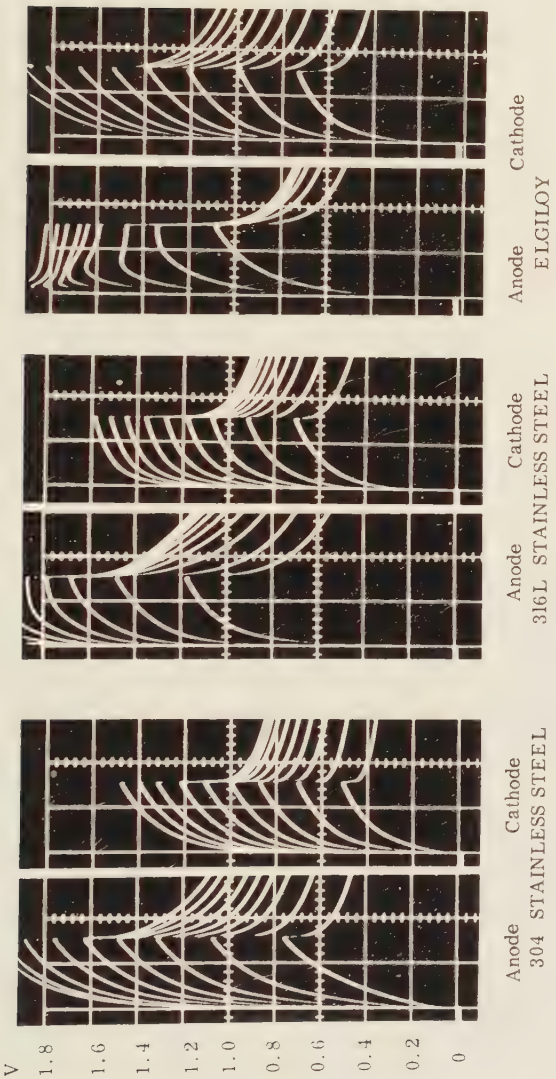

Fig. 3. Non-noble electrodes; horizontal scale intervals are 1 ms.

TITANIUM

To the best of our knowledge, titanium has not been considered previously for use as a pacemaker electrode. However, after recently observing some usage in Australia, we decided to investigate it further. Our interest was further excited by an increasing usage of titanium for anodal electrodes in the form of pacemaker enclosures in Australia and also for passive pacemaker encasements in the USA.

Figure 4 shows our findings on titanium. Titanium exemplifies a fourth class of electrode metals. It differs in many respects from any of the other classes.

The titanium anode requires a large voltage to accomodate a 1 ma current pulse but the waveform is a nearly perfect ramp. Non-noble metals show a much faster initial rise. The ramp suggests a nearly pure capacitor whose dielectric is formed perhaps by the tough, micro-thin oxide that spontaneously forms on the titanium surface. This ramp is important because it indicates that a large-area active anode, such as a titanium pace-

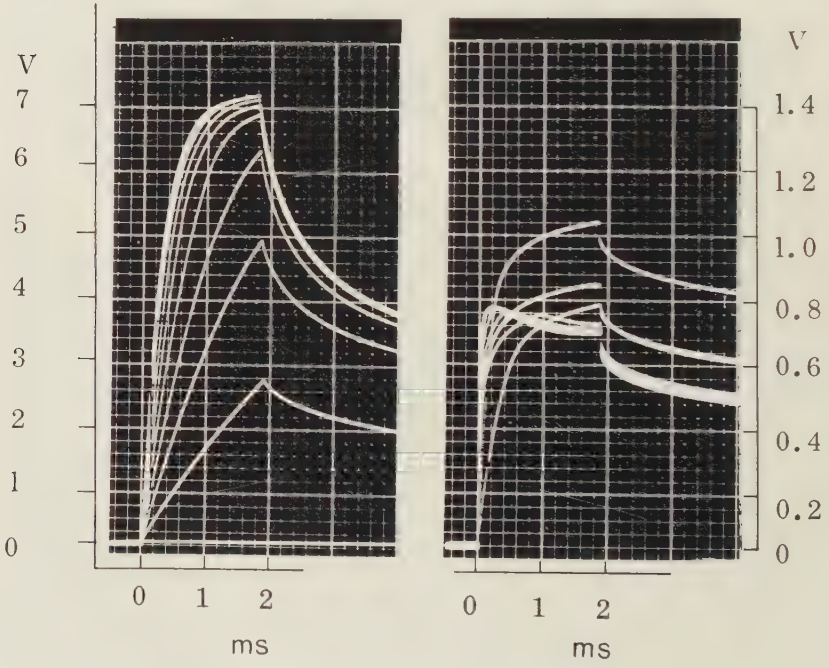

Fig. 4. Titanium electrodes, left-anode, right-cathode.

maker case, could be a very efficient couple to body tissue. The capacity of the ramp in Figure 4 (anode) at 1 ma is:

$$iT = Q = EC \tag{2}$$

$$C = iT/E = \frac{(1ma)(1ms)}{2V} = 0.5\ \mu f \tag{3}$$

Since the electrode was 0.16 cm^2, the specific capacity is about 3 $\mu f/cm^2$. A typical pacemaker case might have 30 cm^2 or more, giving an anode capacity of 100 μf, a respectable coupling, indeed.

The cathode is even more interesting. At low currents, the cathode appears much like the anode, but as soon as about 3.5 microcoulombs have been withdrawn from the cathode (1.2 ms into the 3 ma pulse), the process is suddenly replaced by another which operates at much lower voltages than the first. The transition is seen clearly on the 3 ma pulse in Figure 5. At 4 ma, the transition occurs at 0.8 ms and at 5 ma, at 0.5 ms. At 7 ma, it occurs at about 0.2 ms.

We believe that the initial few microcoulombs in each impulse may strip the oxide from the titanium, leaving a bare titanium surface, which operates at relatively low voltage for the rest of the 2 ms period. After termination

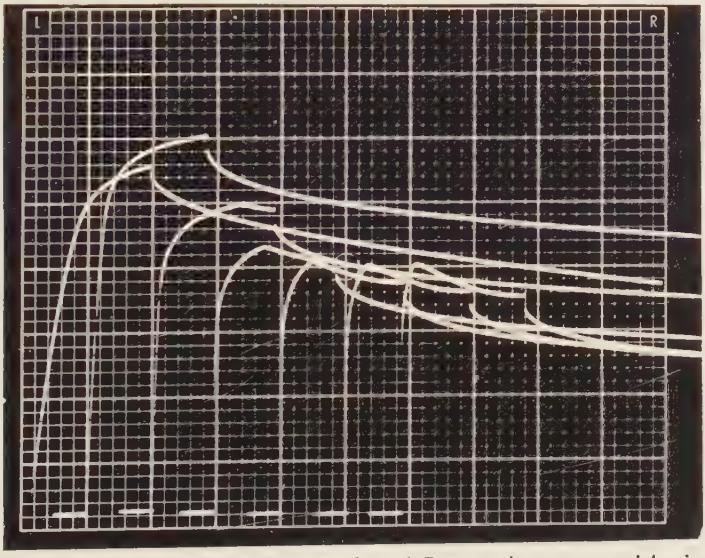

Fig. 5. Titanium cathode. 1, 2, 3, 4, 5, 6, and 7 ma pulses separated horizontally. Vertical scale 1v/major division, horizontal scale 1ms/major division.

of the impulse, the oxide rapidly and spontaneously reforms so that the next impulse begins again with an oxide coated surface. At conventional pacemaker impulse current levels (in the 5 ma range), the titanium cathode compares favorably to platinum in efficiency because of this unusual property. Thus a small geometry cathode coupled with a large geometry anode (pacemaker case) has attractive possibilities from an electrochemical viewpoint. Local foreign body reaction properties have not been investigated by us, however.

Titanium waveforms are rarely exactly reproducible. Both the chemical and electrical history of the surface strongly influence the voltage waveform obtained. Thus, the records shown in Figures 4 and 5 were not precisely reproducible on the following day, even in our high-purity system. However, our general conclusions seem to hold satisfactorily.

We have pulsed titanium anodically and cathodically for thousands of hours and have found no measurable trace of metal ions in solution. In this respect, titanium far excels other non-noble metals and compares favorably to platinum.

CONCLUSIONS

From an electrochemical point of view, all metals we have studied fall into four classes:

(1) Platinum metals are efficient, inert and electrochemically attractive for pacemaker electrodes. They couple by changes in oxygen adsorption. We have used them exclusively clinically. They are not as strong nor as inexpensive as some other metals, however.

(2) Silver metals couple by a reversible, silver to silver chloride process which feeds on the silver anode. We have not used them clinically although others have, with reportedly satisfactory results.

(3) Non-noble metals couple by gas evolution or corrosion processes. They should not be used for small geometry anodes, nor for capacitor-coupled cathodes unless diode cathodic protection is provided. As anodes, area should be kept large and current density low. Even in the latter case some measureable corrosion may occur but may be so low as to be clinically acceptable.

(4) Titanium cathodes, we believe, couple by a reversible stripping of the oxide layer, followed by hydrogen evolution on the bare metal surface. The anode couples at low current density probably by pure capacitive coupling across a microthin, high-dielectric-constant titanium oxide surface. At higher current density, oxygen evolution probably assists.

Our tests indicate titanium to be inert and unreactive, as far as cor-

rosion is concerned, in 37°C physiological saline when driven anodically or cathodically by pacemaker-like pulses.

SUMMARY

Physiological electrodes in body tissue present a complex capacitive impedance load to a pacemaker pulse generator. Nearly all of the capacitive effects occur at the electrode-tissue interface. They vary widely depending on the metal used in the electrode.

These effects may be studied by observing on a fast oscilloscope the complex voltage waveform developed across the electrode-electrolyte interface by a constant-current (galvanostatic) impulse. Such waveforms reveal the chemical reactions occurring at the electrode surface and may aid in identifying those reactions which can, in time, destroy the electrode. Such studies also permit optimizing the efficiency of electrode systems, permitting reliable stimulation with the longest possible battery life.

This paper traced the history of this technique, presented results found in the contemporary literature, and offered some new data suggesting that titanium has desirable properties for use as an electrode.

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20. DISCUSSION OF SECTION II, TRANSDUCER CHARACTERISTICS

Panel: Drs. Francis L. Abel (Chairman), H. Lowell Stone, Warren G. Guntheroth, and Michael F. Wilson

TOPIC 1: Purpose and Goals of the Chronic Preparation

The participants agreed that the perspective of this Symposium certainly dramatized the developments in instrumentation versatility and availability which have occurred over the past decade. The selected approach must still originate with the hypothesis to be tested, but there are now many types of pressure, flow, and dimension transducers. There is a diminishing requirement for each investigator to design his own equipment; this is being done by experts in that area. A somewhat different problem is emerging; now the developing need is for advice and communication on selection of particular transducers for optimal match to the experimental design. A major purpose of this Symposium was to initiate such exchanges. However, the caution was expressed that continued effort was required to avoid the trap of designing an experiment primarily because a certain transducer was available.

The question of the purpose and goals of the chronic animal experiment generated extensive debate. There was a tacit assumption that the chronic preparation was necessary and valuable, providing new information which was frequently different from results obtained with other types of experimental designs such as anesthetized animals. Assuming the investigator posed a problem requiring a chronic animal preparation for its solution, considerable knowledge of available transducers and their characteristics is required. The subsequent discussion of various types of transducers helped to clarify these considerations.

TOPIC 2: Transducer Evaluation

The discussants emphasized the need to evaluate the important properties of all transducer systems in the laboratory where they are being used and as nearly as possible under the conditions in which they are to be used. There was agreement that this was probably not done as often as it should

be, and the manufacturer's specifications should not be the only guide. Rarely an instrument may be damaged in shipping; the earlier this is detected, the better. Occasionally instruments intended for use in fluids have been tested only in air; this is not sufficient. The need for calibration is not so much that the instrument is inherently bad as the fact that there are many ways in which it may be damaged in the course of its use. It is a matter of taking sensible precautions because malfunctions occur within a very short period of time and may remain undetected unless appropriate tests are performed. For instance, the indication of a broken wire in a pressure transducer may be poor zero stability following loss of temperature compensation, even though the pressure waveform appears satisfactory. Therefore periodic rechecking of the status of a given transducer is essential if reliable data are to be obtained.

TOPIC 3: Pressure Measurements

Further discussion of pressure transducers revolved around calibration considerations. Available intravascular pressure transducers are apparently reasonably acceptable. They have very stiff diaphragms and high resonant frequencies and are available in numerous models. Improved zero stability and decreased sensitivity to temperature effects are the major areas in which further refinements could be made. A good combination for true differential pressure measurement in various body cavities would be extremely useful.

Linearity and frequency response are generally excellent. There was unquestioned general agreement that zero drift is inevitable. Typical values are 3 to 10 mm Hg a month when implanted. If precise values are desired, the implanted gauge *must* be periodically calibrated acutely using a standard, reliable method such as a catheter-manometer system. If time relationships are important, phase shifts must also be known.

The most difficult calibration problem is a suitable technique for testing frequency response. Balloon pops and catheter or transducer taps and thumps have poor reliability and reproducibility. A suggested simple technique for simulating a square-wave input is to use a partially withdrawn 30 ml syringe. After connection to the transducer system, withdraw it a small additional amount and let it pop. This generates a square wave that can be evaluated by the usual techniques. One must be very careful that the transducer can tolerate the negative pressure generated by this procedure. It is similar to a balloon pop, but easier and a bit more reproducible. There is much less of a problem with the frequency response of catheter-tip or implantable gauges than with catheter-manometer systems. The implantable

and catheter-tip gauges have resonant frequencies far above the physiological frequencies of interest. A recently introduced sinusoidal oscillator made from a speaker and Lucite tube is proving valuable for testing catheter systems. If a catheter system is the only one used for the measurement, it *must* be evaluated both before and after the test.

The characteristics of an external system for checking an implantable gauge are less stringent if one is only interested in mean pressure, but mean pressure is a function of dynamic pressure, and if that isn't being accurately recorded, the accuracy of the mean value is reduced. Occasionally a massive overgrowth of endothelium or fibrous tissue will distort the pressure wave recorded by an implanted gauge and a suitable catheter-tip or catheter-manometer system will be necessary to distinguish between such artifacts and valid changes.

Gauges placed in a major artery are easier to check. Ventricular placements require either retrograde catheterization or a chronically implanted atrial catheter. Mean left atrial pressure and ventricular end-diastolic pressures have been shown to be close enough to provide an appropriate check.

Most of all, whatever the merits of derived pressure variables such as dp/dt, the variable will fall into disrepute if the original measurement is inaccurate or distorted. The instrument characteristics are critical in such applications.

An added note was to avoid implantation or catheterization altogether. A 21 gauge thin-walled needle of a scalp vein set inserted into a carotid loop was reported to give good pressure measurements.

TOPIC 4: Flow Measurements

The electromagnetic principle seemed to be preferred whenever it could be applied. Problems with such factors as probe mass, vessel erosion, and expense make it a far from ideal technique. Of the alternatives, the ultrasonic Doppler instruments are clearly the logical choice but the properties and uses of these instruments remain less well understood. Accordingly the proponents and users of ultrasonic flowmeters were intensively questioned.

The term "Doppler flowmeter" is often used as though all the ultrasonic flowmeters were identical, which is far from the real situation. A distinct drawback to the ultrasonic Doppler is its susceptibility to "mismanagement" in several respects. There were various opinions of the amount of training and experience required for successful use of the instrument, but there was general agreement that this system is probably

one of the most difficult in which to detect erroneous results. Considerable experience, judgment, and understanding are required to use any of the measurement systems under discussion, but the ultrasonic Doppler flowmeter may be the most difficult one.

There are criteria, however, which if properly followed will reduce the probability of error to levels comparable with other flow measurement techniques. The signal-to-noise ratio should be carefully evaluated and defined, the FM receiver must be properly modified to remove the output de-emphasis network, the readout must be a true wide-band zero-crossing frequency meter, and the calibration must be linear in both in vitro and in vivo tests. The signal-to-noise voltage ratio should be about 10:1. The audio output from a signal with a 3:1 ratio sounds good, but it is inaccurate in a zero-crossing circuit. An appropriate procedure for testing measurement reliability is to begin with the zero-crossing detector sensitivity set at zero, and then increase its sensitivity and observe the effect on the signal. If there is a plateau area where the output is unaffected by changes in detector sensitivity, then the results are reliable. If the discriminator is not saturated, it will be sensitive to signal voltage level and its output is non-quantifiable. Signal-to-noise ratio problems could account for the observation that in high-flow states such as exercise, the signal from an aortic flow transducer may move above the baseline. Obviously the flow velocity does not actually become continuously positive. Theoretically the back-scattered energy is constant, but at high flow velocities a greater percentage of the particles have high energy levels, there is a shift in the back-scattered frequency spectrum, a significant noise level which entered into the discriminator setting at low flows is now insignificant, and the previous discriminator sensitivity is no longer appropriate. The technique for avoiding this is to have the maximum possible signal-to-noise ratio in the resting situation. Care must also be used in setting the discriminator band-pass. A narrow band-pass can decrease the noise and give a suitable signal at rest, but the higher frequencies occurring with exercise will be lost and the top of the signal will be cut off.

As a general rule, very careful judgement must be used in placement of the ultrasonic sensor on a vessel as large as the aorta. While the net aortic flow velocity in diastole is essentially zero, the erythrocytes are undoubtedly surging back and forth, and the Doppler flowmeter responds to these velocities. The presence of turbulence will give an erroneous signal, and placement of this device just past a damaged valve is inappropriate. In other vessels, the Doppler ultrasonic and electromagnetic flow signals are comparable, with linear calibrations over a 40 to 300/minute range of heart rates, and equivalent results would be expected with a pulsed ultrasonic system.

An added complication is the fact that some commercial frequency-to-voltage converters have been non-linear to a constant amplitude, monotonic signal even without any noise, an unforgivable situation. Modifications in circuitry have made it very difficult to obtain a satisfactory commercial version of the ultrasonic flowmeter and this has not helped solve the problems. There have also been faults in transducer construction. The shells are frequently fragile and the wires do not have the proper strain relief. The lead wire should be epoxied to the transducer body so all the strain is not on the solder joint. A number of investigators have been successful in making their own transducers.

A final precaution is not to attempt measurement of very small differences in flow. More should not be asked of the instrument than it is capable of giving. On the other hand, it has been extremely useful in field work, where telemetry is required, and in behavioral experiments. Alternative signal processing techniques under development, such as the direction-sensing and pulsed Dopplers, may reduce the problems further. Telemetry of the electromagnetic flow signal is equally encouraging and may expand the measurement horizons further.

Dilution techniques for flow measurement are of interest for calibration of implanted transducers, and for long-term use, as the technology for maintaining intravascular catheters improves. A constant heparin drip into the blood stream is required to avoid clotting problems or fibrin deposition on the themodilution catheter, so this technique carries its own particular set of problems. Dilution measurements using radioactivity provide an approach to measurement of flow characteristics within an organ that none of the other techniques can provide. Chronically implanted catheters are tolerated much more readily than hardware and the experiments can be repeated readily. They do not suit non-steady-state experimental designs and there are still some problems with the underlying theory on which the calculations are based. For certain kinds of experiments they are certainly a useful state-of-the-art measurement.

TOPIC 5: Dimension Measurements

The characteristics of the ultrasonic techniques were explored. If the ultrasonic crystals are mounted five cm apart on the endocardium, their characteristics should first be tested in an analogous situation. For example, in a water tank with five cm separation, they can be rotated and moved laterally and vertically and a reasonable estimate of directionality can be determined. Design modifications can be evaluated in a similar way so that the final result lies between a very narrow, minimally-dispersed beam and

one which is widely-diffused and has little directionality. The direct visualization of the beam in a Schlieren system is of value, but usually the crystal power must be increased to unrealistic levels before the beam can be adequately visualized.

A real advantage of ultrasonics is the high degree of directionality, even with lenses or other modifications to the crystals or in the electronics. The principle holds over short distances such as the two sides of a vessel, or over long distances such as the diameter of the left ventricle or of the liver. The transmitted and received pulses can be seen easily on an oscilloscope and the time-difference can be reliably translated into distance. If the signal is lost, the crystals are not aligned; if the signal is present, the crystals are aligned and the distance measured is a line. The validity of an ultrasonic signal of this type is much less doubtful than the output of most other transducers.

There followed a discussion of the varying reports of cyclic changes in left ventricular internal geometry from investigators using different techniques. The complex internal surface must not be forgotten. The usefulness of a technique for placement of crystals by direct visualization of an open heart lies in the technical advantage of actually lessening trauma to the heart, not merely in an intrinsic improvement in selection of the placement sites because they can be seen. The shape of the open heart is quite different from its shape when filled with blood in an upright, unanesthetized dog. An interest for future research is to determine why some investigators find a decrease in internal diameter in isovolumetric systole, and others an increase. The different findings probably result from what are actually different, not directly comparable, measurements.

Accurate knowledge of dimensions has profound implications for the study of myocardial mechanics, particulary in application of the force-velocity-length concept. A further significance of dimensional knowledge is the effect of reshaping and changes in fiber orientation on the subsequent contractile process. Unfortunately the most refined of the currently available methods are still relatively crude. One suggested solution was to combine high-speed cineangiography (200 frames/sec or more) with computer analysis of the information through multiple, parallel planes.

TOPIC 6: Measurement Precision

The concluding discussion centered around the necessity for greater precision of measurement created by the extensive capability of available transducers. Extensive qualitative data are available from earlier studies. While comparative data alone might still be sufficient for certain experimen-

tal designs, the general preference was for appropriately quantified, normalized data. Granting the continuing technical difficulties, peripheral flow in ml/min/gm of tissue or stroke volume in ml/min/kg body weight or body surface area are the expected expressions for use in comparing results between animals, although per cent change in values may still be sufficient for certain types of experiments, such as studying the effects of drugs.

SUMMARY

Transducer selection must be tailored to the experimental design. When these decisions have been made and the transducer is delivered, adequate maintenance procedures require not only initial evaluation, but continued testing of instrument characteristics. Pressure, flow, and dimension measurements are the backbone of cardiovascular investigation, and each was discussed to emphasize the particular properties of the various systems. The final point concerned the greater measurement precision permitted by the new instrumentation.

III. IMPLANTATION TECHNIQUES

Section Editor: H. Lowell Stone

A. Animal Selection and Preparation for Surgery
B. Operative Techniques
    Catheters
    Pressure
    Flow
    Dimensions
    Multiple Implants
C. Post-Surgical Care of Animals
D. Discussion

21. FACTORS GOVERNING CHOICE OF ANIMALS FOR CHRONIC INSTRUMENTATION STUDIES

Donald C. Sawyer

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The most important factor concerning selection of an animal for chronic study is that it be healthy and remain healthy (1). Animals should undergo a period of conditioning and pre-surgical evaluation before selection for chronic instrumentation. Animals in poor nutrition and/or poor physical condition will be more susceptible to bacterial and viral diseases and substantial loss of money and investigator time will result.

When choosing an animal for study, two major determinations must be made. First, from previous investigations, which animal would be the most desirable from a physiological or pharmacological point of view? Second, which animal would be most conducive to accomplishment of the study? There are a number of circumstances which control the answers to these questions.

Facilities for animal housing must be a primary factor. Adequate space, proper ventilation and diligent animal caretakers are primary requirements for proper care of chronically instrumented animals. There must be good communication between investigator and animal care personnel to avoid undue loss of animals or costly time delays.

The purchase cost of animals must be considered; the cost is directly related to availability. The more popular the animal specie, the lower the original cost of purchase and, most likely, the cost of maintenance. Instrumented animals must be maintained in individual pens which may cost more than group housing.

The experience of the investigator and technical staff are important considerations. Knowledge of animal behavior, methods of restraint, and performance of specific surgical procedures may be controlling factors. Consultation and support services may be available from the animal care facility which would allow an individual to select animal subjects more objectively.

The type of instrumentation required and duration of the anticipated study have considerable influence on the decision for animal selection. The durability of the implanted material is important as body fluids may break down foreign matter faster in certain animals and some animals are more resistant to the effects of external vascular devices, i.e., erosion, and therefore, allow longer periods of study.

An animal may be selected on the basis of previous studies. If the objective of an investigation is on a comparative basis by virtue of a different or improved technique, one must consider the same animal as was used previously.

DOGS

The last reason given above is probably why the dog has been used extensively for chronic instrumentation studies. Dogs are in plentiful supply and readily available. Most investigators used dogs during their training program and are most familiar with their behavior. Research facilities are customarily designed to house dogs, and some of these have been built specifically for chronically instrumented animals. Dogs are easily managed by laboratory and animal care personnel (2). They are usually accustomed to being handled by people and can be readily trained for chronic study. Common diseases such as canine distemper, infectious canine hepatitis and tracheobronchitis are familiar to animal care personnel. Changes in behavior are usually recognized as symptoms of pending disease. Intravenous anesthesia with pentobarbital can be accomplished with relative ease because of the accessibility of peripheral veins (2, 3). Following induction with a thiobarbiturate, the mouth can be easily held open to allow tracheal intubation. With proper equipment, maintenance of anesthesia can be accomplished with inhalation agents such as halothane (Fluothane, Ayerst Laboratories), methoxyflurane (Metofane, Pitman-Moore, Inc.), nitrous oxide, and others (4, 5). Anatomy textbooks for the dog are available (6), plus a wealth of information on cardiovascular physiology.

In general, the dog offers many advantages as a laboratory animal but there are certain disadvantages. The dog has the ability to undo man's work with teeth and feet. Sensor cables, vascular catheters and other devices are usually implanted to exit through skin anterior to the shoulders on the dorsal surface of the neck. The neck is then bandaged to protect the leads and catheters. Another procedure is to bury the leads under the skin or to have them end at the skin surface (7).

The dog appears to be susceptible to bacterial infection around catheters and sensor cables exiting through skin. Bandage changes every 24-48 hours and systemic and topical antibiotics are helpful following aseptic surgical technique during implantation procedures.

CAT

The cat has never reached the same popularity as the dog for use in the laboratory. The most likely cause is its small size. Most investigators prefer to work with animals weighing 30-40 pounds. Although cats are relatively inexpensive and plentiful, they are usually not as tame as the dog and therefore are not as easy to train for chronic studies. Anesthetic procedures for cats are more difficult than for dogs, but this is not an insurmountable problem (8). Two infectious diseases, feline panleukopenia and pneumonitis, are common but may be controlled by vaccination and a clean, well-ventilated environment. The respiratory disease complex may be a problem for cat colonies housed for chronic studies. Chronic cardiovascular studies are relatively uncommon because of the reasons mentioned, and also because these animals react differently to many drugs compared with dog and man (8, 9).

PIGS

The use of pigs for cardiovascular studies has increased during the past few years. Miniature swine have been bred for size and temperament to make these animals adaptable for laboratory use. Several strains of pigs have been selected to have an average adult weight of 135-150 pounds. A symposium was held in 1965 to report uses of swine in biomedical research (10) and others have pointed out advantages of miniature swine for physiological studies (10, 11, 12). Miniature swine are not as available as dogs and are more expensive to purchase than are dogs from pounds. However, when compared to purebred adult dogs, cost is quite similar. These animals must be kept in enclosed runs or pens: therefore, conventional dog cages are not adequate. Pigs require the same amount of care as the dog, and animal caretakers quickly learn their habits of behavior. Miniature swine are not very tame when received from the supplier and therefore should have 1-2 weeks to acclimate to their environment. It is helpful if a caretaker can sit in the pen at feeding time to allow the animals to become accustomed to man. An enclosed transport cage can be used to move animals from pen to laboratory. Ten minutes of placing these animals on a table in the laboratory for a few days before surgery will reduce their apprehensions considerably. They eventually will rest quietly on a table but always in sternal recumbency. Pigs do not like to be picked up and scream quite vigorously before being placed on a table. By putting a ramp between the cart and table, animals can be trained to walk on and off the table.

Intravenous injection for anesthetic administration is difficult because

peripheral veins are not easily identified. Ear veins and recurrent tarsal veins can be used. Pigs strongly object to needle puncture which makes intravenous injections difficult. The use of narcotics and/or tranquilizers as preanesthetic medication will facilitate administration of an intravenous or inhalation agent (13, 14) for anesthesia induction and may be accomplished with little restraint. I have found that halothane, nitrous oxide and oxygen delivered by mask is an effective means for induction and requires minimal restraint. With the exception of perhaps the rabbit, the pig is the most difficult animal for tracheal intubation but it can be accomplished with practice (14, 15). If intravenous injection of drugs is to be done following instrumentation, a catheter implanted in a peripheral vein will be helpful. The internal mammary vein, jugular vein or femoral vein can be used and will alleviate the need for arduous venoclysis. The short hind legs and vascular anatomy make femoral artery and vein cannulation more trying for the unskilled surgeon. Also, thick tissue layers and differences in thoracic anatomy make thoracotomy and flow sensor implantation procedures longer in duration (16, 17). In addition, swine will continue to grow. Controlled feeding can be used to slow the growth rate but it is possible for these animals to grow out of their instrumentation.

A specific advantage that pigs offer is that the skin opening through which the catheters pass heals quite well. Pigs do not have good mobility of their feet and head and therefore cannot reach catheters and sensor leads exiting on the dorsal surface of the back. They will rub against objects; therefore, low door openings should be avoided. Pigs should be housed individually and animals in adjacent pens should not have access to each other. One pig will cooperate with another to allow removal of bandages. The use of a tubular stockinette as a shirt with two holes cut to allow room for the front legs provides protection from rubbing.

NON-HUMAN PRIMATES

Non-human primates are being used for chronic instrumentation studies with increasing frequency. A well-developed central nervous system, a more desirable cerebral vascular circulation, and general physiology make these animals useful for many investigations. Primates do have certain disadvantages. Their cost for purchase and maintenance is relatively high, and availability may be a problem. They require special handling and restraint should be performed by trained personnel (18). Special considerations may be necessary for certain investigations depending on the size and specie used for study. For chronic instrumentation studies, it is desirable to allow these animals to move freely in individual cages. Application of telemetry systems

is very appropriate where restraint for long periods may be undesirable or impossible. Extreme care with bandage application must be taken as they can be removed with ease. Primates are particularly susceptible to respiratory diseases, especially tuberculosis, and to viral and parasitic infections. Prophylactic procedures should be made to maintain a healthy colony. Anesthetic procedures are not difficult and once restrained, peripheral venous injection of anesthetics is relatively easy (18, 19, 20). Tracheal intubation is not difficult and maintenance of anesthesia does not present any specific limitation. The anatomy of the ascending aorta is somewhat different in the primate and one must be sure that the desired instrumentation will fit. Non-human primates can be extremely useful for cardiovascular studies but animal care facilities must be properly equipped and managed for successful long term studies.

RUMINANTS

Ruminants, such as calves, sheep and goats are used for a variety of cardiovascular studies but are commonly used for cerebral blood flow and fetal circulation investigations. As with pigs, special housing arrangements should be made. To obtain good quality animals, costs may be relatively high. These animals are usually easy to restrain and are content to rest quietly for long periods, i.e., 24 hours. Calves, sheep and goats can be studied continuously for periods lasting a week or longer. External catheters and sensor leads are not bothered by these animals and long term studies are more feasible. Calves appear to survive cardiopulmonary bypass procedures for cardiac surgery better than other animals (21). Rapid formation of fibrin may occur on implanted intravascular devices. Calves continue to grow which may be a disadvantage for some investigations. Special considerations should be given for anesthesia as regurgitation will occur during tracheal intubation and throughout the anesthetic period (22, 23), as will gas production in rumen. With the exception of pigmy species, these animals may exceed 100 pounds and laboratory space must be considered. For surgery, the lateral recumbent position is preferable. The large abdominal viscera restrict diaphragm movement and reduce venous return through the inferior vena cava when the animal is in dorsal recumbency. An interesting use of sheep for chronic instrumentation is for study of pulmonary lymphatic circulation. Large lymphatic vessels can be isolated and cannulated.

PONY

The pony may be considered for chronic intravascular instrumentation in a laboratory environment (24, 25). Stall or pen type housing is required

in the animal care facility as would be needed for ruminants. Because the pony is not a common research animal, references concerning normal physiology are not readily available. Cardiopulmonary bypass procedures can be accomplished in the pony.

SUMMARY

It is obvious that the ideal animal for cardiovascular instrumentation has not yet been found. There are certain advantages, disadvantages and limitations of each animal specie which will make it more or less desirable for a specific situation. Some of the factors involving animal selection have been presented which may assist in the objective selection of animal subjects for chronic cardiovascular instrumentation.

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22. PREOPERATIVE PREPARATION OF ANIMALS FOR CHRONIC CARDIOVASCULAR INSTRUMENTATION

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Preoperative preparation encompasses the total activity provided to make the patient safe for the operation so that the operation will be safe for the patient. In an experimental situation, preoperative preparation begins with the selection of candidates for a particular investigation and extends unto the actual time of surgery. Appropriate preoperative preparation takes into consideration every essential detail of the operative procedure. In this regard, attention must be given to the surgical approach to be employed, the instrumentation to be implanted, the approximate duration of the operative procedure, and the possible operative and postoperative complications which may arise.

SELECTION OF CANDIDATES

The degree of success achieved in instrumenting animals for chronic cardiovascular studies depends in part upon the selection of animals vigorous enough to withstand the stress of cardiac surgery. Such factors as general health, body conformation, genetic background, age, sex and temperament are important considerations in the selection of candidates. In most research facilities animals are obtained from dealers or from pounds, and little is known about their genetic background. Fletcher (1) has suggested the existence of stress resistance patterns in dogs of a particular breed. In his studies he compared the survival rates between pure-bred and random source dogs that were subjected to cardiac surgery. The results of his studies indicated that the survival of pure-bred Labrador retrievers undergoing heart valve replacement was 93%, while that of conditioned, healthy pound dogs of similar size was 73%. He concluded that the use of pure-bred, healthy animals in research reduces the number of variables in the experiment, decreases the overall cost of the experiment, and assures

the availability of appropriate experimental animals when needed.

There are often consistent differences in temperament and response to handling between types of animals within a species. Therefore selections for studies involving conscious animals should be made from breeds noted for low aggressiveness and ease of training whenever possible.

QUARANTINE AND CONDITIONING

All animals used in chronic cardiovascular studies should be quarantined for a period of at least two weeks. In the case of subhuman primates, the period of quarantine is extended to a minimum of six weeks, to provide adequate time for a tuberculosis testing program. It is important that ruminants and swine be obtained from certified brucellosis-free herds.

Upon arrival, each animal should be given a careful physical examination by a veterinarian. Dehydrated, emaciated animals or those having symptoms of cardiovascular, respiratory, or systemic disease are rejected. Primates must have been certified free of tuberculosis by a veterinarian at the commerical source within ten days preceding arrival. Ruminants are especially sensitive to changes and irregularties in feeding and watering while in transit. Any dietary change directly disturbs the ruminant's complex digestive system, resulting in partial or complete anorexia and the attendant lowered resistance to infection. Calves and sheep should therefore be observed carefully for the first week following arrival for evidence of shipping fever complex. At some facilities, prophylatic antibiotics are administered during this period. If external parasites infest members of any species, the animals should be dipped, sprayed or dusted with the appropriate ectoparasiticide.

Fecal samples should be examined microscopically for the presence of internal parasites. Infested animals should be treated with the appropriate antihelminthic or antiprotozoan drug during the quarantine period. Ruminants and swine exhibiting moderate to heavy infestation of lungworm ova in the feces should not be subjected to cardiac surgery, since lungworm infection may cause verminous pneumonia or lead to viral or bacterial pneumonia. In swine, lungworm larvae may serve as vectors of influenza virus.

Blood studies are important in establishing the normality of an animal population. All candidates for cardiovascular surgery should be given a complete blood count while the animal is in the quarantine period. Slides used for differential counts should also be examined for protozoan parasites of the blood.

Of the parasites infesting the canine species, perhaps the heartworm

(Dirofilaria) is the most troublesome, depending upon the particular area of the country from which the dogs are derived. This parasite can cause extensive problems for people utilizing the dog in cardiovascular experiments. Therefore, blood samples from dogs should be examined for Dirofilaria larvae while in quarantine. Several methods are available for detecting the microfilaria in the peripheral blood. Microfilaria may be concentrated by collecting serum from a clotted sample, or by hemolyzing the erythrocytes with a dilute solution of saponin. The latter technique is preferred and the procedure is as follows: 3 ml of a 3% solution of saponin is mixed with an equal volume of noncoagulated blood. The mixture is allowed to stand for five minutes and then centrifuged for five minutes at 2000 r.p.m. The supernatant is then decanted and a drop of the sediment is examined microscopically. Since the saponin does not kill the microfilaria, they can be seen actively thrashing about with a series of kinky movements. Altman (2) has described a rapid, highly effective microfilaria survey procedure for use in large colonies which is highly effective for detecting heartworm larvae in the blood. The method consists of microscopic examination of the buffy coat of a capillary tube after centrifugation for hematocrit determination. This examination should be made immediately following centrifugation as the microfilaria tend to migrate into the plasma. It is possible, however, to inhibit this migration by freezing the sample, and within a period of four hours the sample may be thawed and examined. It is of interest that studies of the periodicity of Dirofilaria larvae in peripheral blood have revealed that they are present in greatest numbers at midnight and in least numbers at 10 A.M., and that the greatest number is 6.5 times the least (3). Different methods have been used to concentrate the number of microfilaria in the peripheral blood. Young (4) recommends the intravenous injection of 1.0 to 1.5 ml of a 1:10,000 solution of epinephrine hydrochloride to increase the number of microfilaria in the peripheral circulation. Microfilaria other than those of the Dirofilaria species also occur in the blood of dogs, such as the larvae of Dipetalonema reconditum. Differentiation by means of morphological characteristics is required when microfilaria are found.

IMMUNIZATION

Prophylactic measures should be taken to prevent the occurrence of infectious diseases during the time course of a chronic experiment. Dogs should be immunized against distemper, hepatitis and leptospirosis during the period of quarantine. To confer strong immunity against these diseases we have routinely given two inoculations two weeks apart to such dogs. Swine should be immunized against erysipelas, a disease of this species

which is also transmissible to man. The formalin killed bacterium is safe for this purpose and it cannot infect other species of animals nor man. Members of the equine species are especially susceptible to tetanus, and a high incidence of this disease is also seen in sheep and goats. It is advisable in these species to immunize against tetanus or administer the antitoxin a day or two prior to surgery.

BLOOD TYPING

It is often advisable during the preoperative period to identify potential blood donors for any necessary postoperative blood transfusion. To date, 11 blood group systems have been identified in cattle, 7 in sheep, 8 in horses, 14 in swine and 7 in dogs. Unfortunately, reagents for the blood-typing of animals are not commercially available. It is possible, in many instances, to determine compatibility by cross-matching blood from potential donors and recipients.

The bovine possesses an inherent inagglutinability of erythrocytes. This has been postulated to be due to an inward position of the antigens on the red cell surface, rather than to an incompleteness of the antibodies (5). Hence, complicated lytic techniques are used for blood-typing cattle. Fortunately, very few isoagglutinins occur in the normal serum of cattle so that few transfusion reactions occur. The anti-J reaction is the usual cause. Since only the very young of this species are used in cardiovascular studies, it is advisable to obtain blood from the dam a day or two preceding surgery. For cross-matching, the tube test is preferred to the slide test for detection of hemolysis and isoagglutination.

FINAL PREPARATIONS AND PREANESTHETIC MEDICATION

All candidates for cardiovascular instrumentation should be fasted for varying periods of time preceding surgery. In the case of simple stomached animals, this may be accomplished by withholding food for 24 hours and water for 12 hours prior to the scheduled operation. Ruminants should be fasted for a longer period of time, preferably 36 to 48 hours, depending upon the nutritional state and age of the animal. Water should be withheld only for the 12 hour period preceding surgery. Since the rumen will still contain considerable ingesta undergoing fermentation, an oral-gastric tube should be inserted following endotracheal intubation to prevent tympanitic distention of the stomach while the animal is anesthetized.

It is common practice to administer systemic antibiotic drugs to animals selected for cardiac surgery, the rationale being the unavoidability of a

certain degree of bacterial contamination. A therapuetic level of a wide-range antibiotic in the blood at the time of surgery may prevent infection of the exposed and traumatized tissues. Chloramphenicol should not be used for this purpose when barbiturate anesthesia is administered. Teske (6) demonstrated that chloramphenicol administered to dogs orally, intramuscularly or intravenously prior to or concurrently with pentobarbital-induced anesthesia consistently resulted in prolongation of the duration of anesthesia. This response was suggested to result from inhibition of the liver microsomal enzyme that inactivates pentobarbital.

Care must be taken, in preparing the skin for the surgical procedure, to avoid the use of products which are antagonistic to each other. The quaternary ammonium compounds are most effective in their aqueous form, but soap neutralizes the effect of these compounds, hence, they should be used following a detergent scrub or after removing the soap with alcohol. Soaps or detergents containing hexachlorophene exhibit a residual bacteriostatic action against the resident bacterial flora. However, alcohol counteracts the bacteriostatic effectiveness of hexachlorophene so that the two should not be used together (7). Iodine or mercurial disinfectants are suitable to use following a hexachlorophene scrub if desired. We have been unable to demonstrate resident bacterial flora on the skin of animals prepared by a detergent scrub followed by 70% alcohol and then a final application of thimerosal tincture (Merthiolate, Eli Lilly).

Preanesthetic agents are frequently used in experimental cardiac surgery to reduce parasympathetic stimulation and to prevent salivation, laryngospasm, bronchospasm, and cardiac slowing, and to cause a smooth recovery from anesthesia. The last mentioned purpose is especially important since many surgical endeavors can be nullified if the excitement stage during anesthetic recovery is not mitigated. The following summaries list the preanesthetic medications which I have found beneficial in animals subjected to cardiac instrumentation. A conscious effort has been made to avoid pharmacomania. The information on nonhuman primates was obtained from the literature.

Canines

Dogs are premedicated with atropine (0.05 mg/lb) administered intramuscularly. As a prophylactic against the development of arrhythmias during surgery, an intramuscular dose of 100 mg of xylocaine is given. A 500 mg dose of sodium ampicillin is administered intramuscularly. Since we routinely use barbiturate anesthesia in this species, the use of corticosteroids and the intravenous administration of glucose during surgery is con-

traindicated. Elevation of the blood sugar level prolongs sleeping time in animals anesthetized with barbiturates (8).

Ruminants

Calves are given an initial intramuscular injection of 10 mg of atropine, while adult sheep and goats are given 15 mg of this drug. In ruminants multiple doses of atropine may be required during anesthesia to prevent excessive salivation, in which case one half of the inital dosage is used for additional injections. In ruminants, barbiturate anesthetics produce excessively prolonged sleeping times and therefore are not recommended. This is true of even the ultrashort acting barbiturates and therefore halothane is preferred for induction and maintenance of anesthesia in these species.

For induction of anesthesia, a face mask may be fashioned from a plastic bottle of appropriate size. A therapeutic dose of prednisolone, administered preoperatively, has been found to be of benefit in preventing shock in calves. For prophylactic use before surgery, an intramuscular dose of 1 gm of procainamide is given to calves and sheep to prevent the development of arrhythmias, and 500 mg of oxytetracycline is given to prevent infection.

Swine

Swine may be atropinized with 0.04 mg of atropine per pound of body weight. Intramuscular injections of aqueous penicillin (1,000,000 units) are given as a prophylactic to infection. Anesthesia in this species is induced with a 2.5% solution of thiopental administered through an ear vein and maintained with halothane following intubation. Endotracheal intubation may be aided by anesthetizing the vocal folds with lidocaine.

Nonhuman Primates

The major problem in anesthetizing primates lies in restraint of the animals. A squeeze cage should be used for this purpose. Phencyclidine (Sernylan, Parke Davis) is used as a preanesthetic to produce a cataleptoid state (9). The dose producing this response in both monkeys and chimpanzees is 0.6 mg/kg. An intramuscular injection of 0.5 mg of atropine is usually administered to the chimpanzee. Anesthesia may be induced with a 2% concentration of halothane using a face mask.

Horses

Horses are tranquillized with promazine. The dosage is 0.5 mg/lb and is given by slow intravenous injection. Atropine is injected intramuscularly (40 mg). Surital (Parke Davis) is administered to induce anesthesia in this species using a 5% solution. Anesthesia in this species consists of a 30% oxygen, 70% nitrous oxide mixture passed through a halothane vaporizer adjusted to produce a concentration of 0.5 - 1.5%. Five grams of oxytetracycline are given by slow intravenous injection. Horses are not given antiarrhythmic agents preoperatively, but 15 ml of a 5% solution of cyclaine is made available for topical application on the heart during surgery (10).

SUMMARY

For successful cardiovascular instrumentation in experimental animals, considerable attention must be given to the selection of candidates able to undergo the stresses of cardiac surgery. These candidates must then be subjected to special care and treatment for sufficient time to stabilize and where necessary, to improve their health to make them suitable for chronic research purposes. Such a program represents a major portion of the preoperative preparation and should be given ample representation in the experimental design.

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23. A CHRONIC INDWELLING VASCULAR CATHETER FOR BLOOD SAMPLING AND PRESSURE MEASUREMENT

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A common problem in chronic cardiovascular instrumentation is providing an external site for blood sampling and intravascular pressure measurement (1-3). A variety of complex and expensive indwelling catheters have been described previously for chronic arterial and venous cannulation. It was felt that the ideal indwelling catheter should have the following characteristics:

Indwelling arterial catheters should be:

1. Inexpensive and easy to obtain. Many of those which have been described in the literature require complex machining and preparation before use.
2. Simple to use and require minimal care.
3. Rigid enough to provide a faithful transmission of pressure changes, yet flexible to prevent kinking and breakage and damage to cardiovascular structures.
4. Clot resistant.

These requirements can be met by using a 5 Fr. premature infant feeding tube (Davol No. 3640, Davol, Inc.). The catheter is 15 inches in length and equipped with a soft polyvinyl Luer-lock type of connector which has an attached plug.

The catheter as purchased is shown on the left in Figure 1. Several modifications are made. When purchased, the catheter has only multiple side holes, with the end blocked. So the end is cut off, leaving one side hole and an end hole. This helps insure that each flushing will clear the end completely.

The other end, which will be exteriorized, has a soft rubbery connector. In order to prevent breakage due to flexing, an oversized piece of polyvinyl

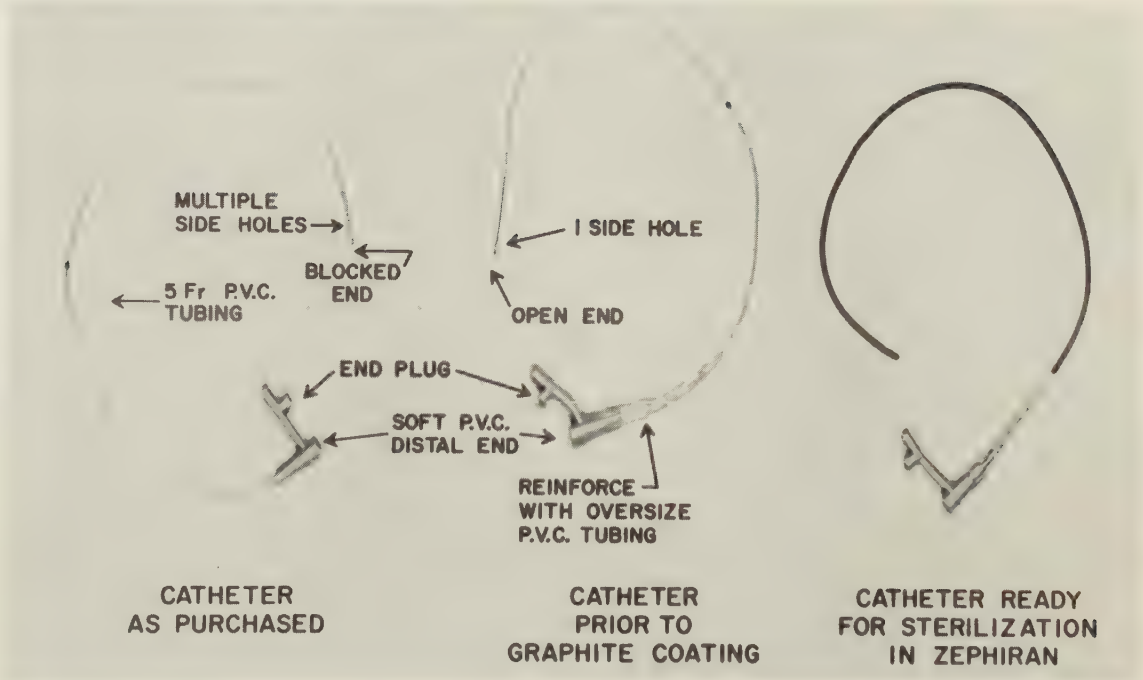

Fig. 1. Modifications of the premature infant feeding tube prior to use as a chronic indwelling catheter.

tubing is slipped over the catheter tubing and cemented in place at the external end with xylene. The exteriorized end is held in place by passing a 2-0 Tevdec suture through the skin and tying the connector down to the dog's back.

Finally the catheter is given a graphite, benzalkonium, and heparin (GBH) coating as originally described by Gott and his group in 1963 (4, 5). The surface coating is produced as follows: The polyvinyl chloride tubing is dipped in a vertical column filled with "Dag 154 graphite," (Acheson Colloid Co.) diluted 3:1 with tetrahydrofuran, for a maximum of 10 seconds. It is then immediately removed and dried by blowing air through the catheter. The process is repeated twice. The catheter is then allowed to dry at room temperature for a minimum of 4-6 hours, before use.[2]

The catheter is prepared for implantation by total immersion for 24 hours in a 1/1000 mixture of benzalkonium or Zephiran chloride (Winthrop Inc., New York, N.Y.). This will sterilize the catheter and prepares the surface for the final layer, which is the adsorbed heparin. After removing the catheter from the benzalkonium, it is rinsed in sterile saline and then immersed for 2 hours in a sterile solution containing 1000 U/ml of heparin.

The catheter is now ready for implantation in an artery, a vein or any of the cardiac chambers. The catheter may be implanted through a small hole in a vessel wall using a purse string suture around the hole to tie the catheter in place. In other areas a vessel branch may be cannulated and the catheter tip advanced into the main vessel. Finally, catheters may be placed in the atria or ventricles of the heart through stab wounds which are then closed with purse string sutures and pledgets. There is one point that must be emphasized. Wherever the catheter tip is placed, it must be in a moving stream of blood. If stasis is produced in any vessel of the body, the blood may clot whether a catheter is present or not. Therefore the catheter must be positioned so that there is no dead space around the catheter tip, and it must be in a moving stream of blood.

After the catheter tip is implanted, the rubber Luer-lock end is exteriorized through a tunnel under the skin to the dorsal midline. This rubber end has been found to be relatively non-irritating to the animal's skin and because of its light weight, the animal tends to forget about it. The exteriorized end may be attached directly to a strain gauge for pressure measurement or a syringe may be attached for withdrawing blood samples. At the end of an experiment, the catheter is flushed with heparinized saline and then the investigator pinches the soft rubber end with the fingers while

[2] *Ed. Note:* A recent development in anticoagulation processes is based on a tridodecylmethylammonium chloride (TDMAC)/heparin complex and is used widely. Details are available from Battelle Laboratories, 505 King Ave., Columbus, Ohio 43201; the TDMAC complex is supplied by Polysciences, Inc., Warrington Penn. 18976.

removing the syringe and replacing the attached plug. This prevents back flow of blood into the end of the catheter. If the catheter is not used for several days it should be flushed with saline and refilled with 1 ml of 1000 U/ml Heparin. 111 catheters were prepared as described and were implanted in dogs in our laboratory.

Table I lists the vessels and cardiac chambers which were utilized. These animals were used for a variety of studies in our laboratory and some were sacrificed or expired during the study. Consequently the survival time of the dog is compared with the length of time the catheter remained patent.

In some complex surgical procedures, it is desirable to give intravenous fluid during the surgery and for 1-5 days postoperatively. To avoid making multiple venous punctures in 27 dogs, a catheter prepared as previously described was implanted in the cephalic vein of the front leg at the time of surgery. The Luer-lock end is exteriorized and taped to the dog's leg. The catheters were used for intravenous fluids and for withdrawing blood samples for 1-5 days and were then removed. For this reason no average survival time is listed for the dogs with catheters in this vein.

In 20 dogs, catheters were implanted in the left atrium and left ventricle during cardiopulmonary bypass (6). These animals had a mitral prosthesis and an attached electromagnetic flowmeter implanted. The two

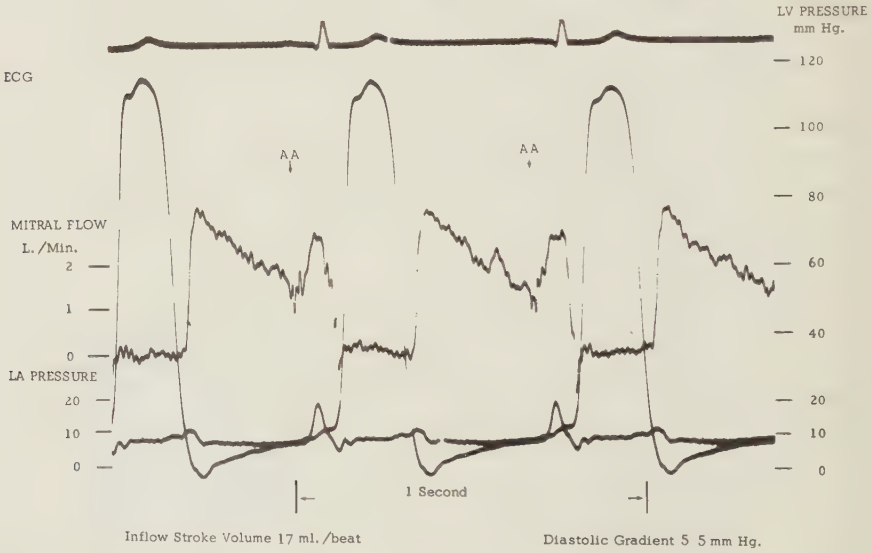

Fig. 2. Mitral flow through a 25 mm Starr-Edwards low profile discoid valve. Reproduced, by permission, from the *Journal of Thoracic and Cardiovascular Surgery*, 61:235, 1971.

catheters were used to measure the pressure in the left atrium and left ventricle simultaneously.

Figure 2 shows the left atrial and left ventricular pressure recorded seven days after the prosthetic mitral valve and catheters were implanted. Zero flow occurs at the reversal of left atrial and left ventricular pressure, and ventricular filling begins when left ventricular pressure falls below left atrial pressure.

A catheter may be implanted through the wall of the aorta for systemic pressure measurement. With the tip in a rapidly moving stream of blood, the catheter will remain patent for periods up to eight months. An example of the quality of the phasic pressure tracing is shown in Figure 3. A catheter was implanted in the descending thoracic aorta along with electromagnetic flow probes on the ascending aorta and the left circumflex coronary artery. The record was obtained 22 days after catheter implantation.

This type of catheter is also commercially available in a larger 8 Fr. size. The larger catheter may be implanted as described and used for angiography and dye dilution curves.

Table I - 111 GBH COATED CATHETERS IN EXPERIMENTAL ANIMALS

Vessel or Cardiac Chamber Utilized	Number of Catheters Tested	Average Survival of Dogs (in days)	Average Time Catheter Remained Patent (in days)	Number of Catheters Which Clotted
Carotid Artery	6	31	17	1
Subclavian Artery	8	39	28	1
Internal Mammary Artery	8	42	14	2
Cephalic Vein Front Leg	27	≠	5	1
Jugular Vein	7	21	15	2
Right Atrium	7	14	11	1
Right Ventricle	4	6	6	0
Left Atrium	22	21	17	4
Left Ventricle	20	25	20	3
Splenic Vein	12	72	54	1

≠ The catheter was routinely removed by the fifth postoperative day, therefore the survival time of the dog is not significant.

Fig. 3. Phasic aortic and coronary blood flows, and arterial blood pressure measured using a chronic indwelling catheter in the descending thoracic aorta, recorded 22 days after implantation.

Blood samples may be obtained for blood gas analysis, electrolyte determination or complete blood counts. In addition the catheter may be used to obtain blood samples for serial Lee-White clotting times to monitor Heparin therapy in animals with implanted prosthetic valves. It is necessary to flush the catheter with saline and then withdraw some blood through the catheter before the sample to be tested is withdrawn.

SUMMARY

A 5 Fr. infant feeding tube can be modified slightly and used as a chronic indwelling catheter. These catheters may be implanted in arteries, veins or any of the cardiac chambers. They will remain patent from weeks

to months with minimal care. The soft rubber connector which is exteriorized is not as irritating to the skin as more bulky epoxy or plastic connectors. The catheters may be used for withdrawal of blood samples, intravenous infusions, or may be connected to strain gauges for chronic pressure measurements.

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24. ARTIFICIAL SIDE-BRANCHES FOR INTRAVASCULAR SAMPLING

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The technique of cannulating arteries lacking readily available side branches by means of a device externally applied to the vessel was first developed in our laboratory (1, 2) as a method of measuring blood pressure without interfering with blood flow in the artery. The need for such a technique is particulary acute in experiments concerned with the investigation of blood flow in the arteries forming the circle of Willis, which is located at the base of the brain. In the dog these arteries are one millimeter or less in diameter, and the insertion of a cannula may seriously obstruct blood flow. In prior studies we had attempted to measure blood pressure by using either a T-cannula (3) or by cannulating an available side branch (4). Neither procedure was as uniformly successful as the technique we termed "external vertical (EV) cannulation".

The cannulas are constructed by hand from short lengths of silicone or polyvinyl chloride tubing (Table 1, Fig. 1). Sets of cannulas with calibers which approximate the diameters of the arteries to be studied can be conveniently made up in advance. The short, unconnected end of the cannula is sealed by plugging it with a tightly fitting piece of either stainless steel or plastic solid, which is glued in place (1). The metal plug is superior to the plastic, for it gives more stability to the cannula, is more firmly held by the glue, and allows the use of a shorter end. If the cannula is cold sterilized, the plug may need to be reglued just before use. The exposed artery (¼ - ½ inch) is first carefully examined for side branches. Any branches present should be ligated or cauterized; cautery is preferable as it leaves a smoother surface than a knotted ligature. The connective tissue must be carefully stripped from the artery over the entire area where glue is to be applied; the total length of the stripped area should include the I.D. of the cannula plus from 2 to 5 mm on either side of the cannula. The adhering tissue can be loosened with curved iris forceps with teeth and can be cut from the artery with iris scissors. To test for the satisfactory removal of this tissue the

TABLE 1

Specification of Tubing			I.D.		O.D.	
Cannula			in.	(mm)	in.	(mm)
Extra Small:	Dow Corning "Silastic"	#602-201	0.040	(1.02)	0.085	(2.16)
Small:	Dow Corning "Silastic"	#S-24934	0.037	(0.94)	0.110	(2.79)
Medium:	Nalge "Nalgon"		0.06	(1.6)	0.19	(4.8)
Large:	Nalge "Nalgon"	#8000	0.19	(4.8)	0.31	(7.9)

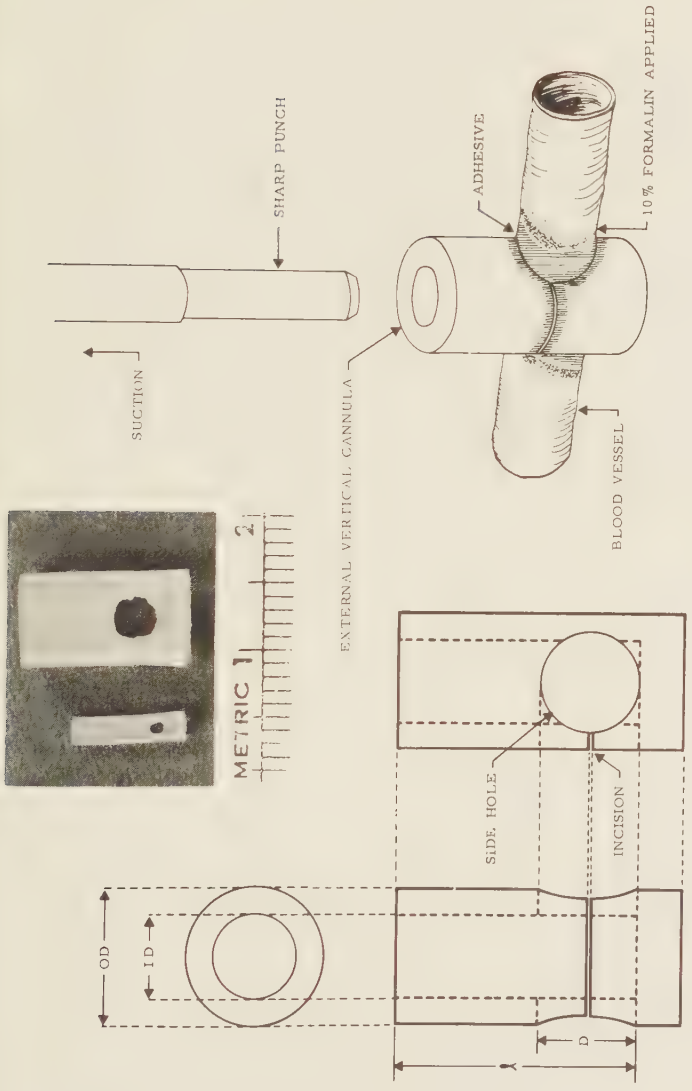

Fig. 1. A: Schema of external vertical cannula. B: Drawing of technique of external vertical cannulation. Note that inside diameter of cannula, which is about half its outside diameter, is approximately the same as inside diameter of the artery. Insert: hand-made cannulas used on the superior thyroid, basilar, and posterior communicating arteries (left) and on the common carotid artery (right) in dogs. Reproduced, by permission, from the *Journal of Applied Physiology* 28:702, 1970.

artery is flooded with saline which is then drawn off by gentle suction. If excess connective tissue still adheres to the artery, the surface has a whitish and relatively dull appearance. Small damp pledgets of cotton held in hemostats are used to tease the connective tissue into a mass large enough to be grasped with the forceps.

When the arterial surface is sufficiently clean, the entire area can be gently dried. A small strip of dry gauze tape or cottonoid passed under the artery will keep the undersurface dry. (Note: this should be removed *after* the cannula is in place but *before* glue is applied). The wall of the arterial segment to be placed in the cannula slit, and of an additional 2 to 5 mm on either side, is then dried with 10% formalin and the artery is inserted in the slit in the cannula. By passing a stylet through the open end of the cannula and applying pressure on it, the slit in the cannula can be forced open and the artery slipped through it and into place. The cannula should approximate the size of the artery, and the hole for the artery should provide a gentle accomodation, that is, it should be just large enough to fit the vessel snugly without compressing it. The glue (either Sankyo's "Aron Alpha" or Ethicon's "Bucrylate") is applied sparingly. We use a bone curet spoon for a container and a sharpened dental probe to apply the glue (Fig. 2). After it is certain that the cannula is pointed as desired, the glue is placed first in the slit, and then at the points where the artery enters and leaves the cannula. Too much glue forms a crust which peels off easily, too little allows leakage. To test for leaks, the area is flooded with saline and gentle suction is applied to the cannula; the appearance of fluid in the cannula indicates a leak.

When the cannula has been made free of leaks, the arterial wall can be punctured. To accomplish this, a short end of needle tubing with a sleeve of plastic tubing placed at about the midpoint is inserted into the end of the cannula. Scored circles around the needle tubing permit the attachment of sutures if needed. Then a sharpened needle with the bevel end removed, the edge honed, and equipped with a special adapter for suction (Fig. 2), is inserted and used to cut a circular opening in the arterial wall and to suck out the disk-shaped piece. If the disk is not completely cut away and some remains, inaccurate measurements of pressure or flow may be obtained, or sampling may be difficult.

After the arterial wall has been successfully punctured, the needle tubing may be used to connect the EV cannula either to a transducer so that blood pressure can be measured or to a cannula arranged so that repeated blood samples can be drawn. It is imperative to have the connections ready at hand and to attach them immediately when the artery is punctured.

Certain steps in this procedure are critical: 1) adequate stripping of the

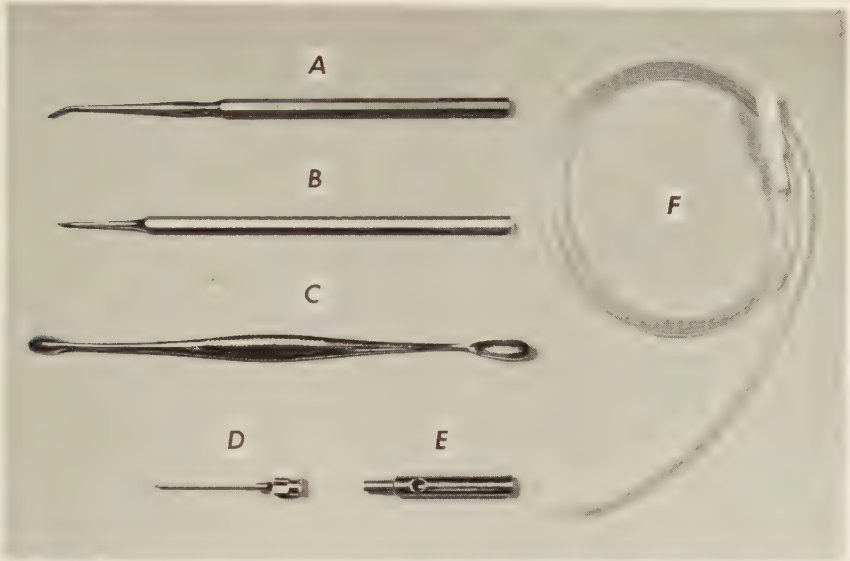

Fig. 2. Instruments for gluing and puncturing the artery. A and B, picks; C, curet; D, needle for puncture; E and F, suction adapters.

artery at the site of the cannula application, 2) firm gluing of the cannula to the artery so that no leakage can occur, 3) complete puncture of the arterial wall and withdrawal of the punched-out fragment of vessel wall, and 4) prevention of clots both in the cannula and in the artery near the cannula opening.

If an animal is to be used for chronic studies, additional precautions have to be taken. Two possible solutions are: 1) a special suture of waxed white cotton is placed on the needle tubing proximal to the plastic sleeve and sewn into the skin, or 2) a collar of silicone is sewn into the skin. The easy retrieval of the cannula in case the animal struggles while it is being cleaned can be a problem. Also the cannula and the connector made of needle tubing should be of a sufficient total length that the tubing protrudes from the incision. If these precautions are observed, a clogged cannula can be cleaned simply by disconnecting and rinsing the tubing attached to the Tuohy-Borst adapter. The artery is then repunctured if necessary.

The wound is closed in the usual manner after a small amount of heparin has been flushed through the cannula to remove any small clots that might have formed. If the location permits, muscle sutures can be used to support the cannula. A dressing cover which protects the incision, but allows the animal maximum freedom, is helpful in protecting the incision and cannula.

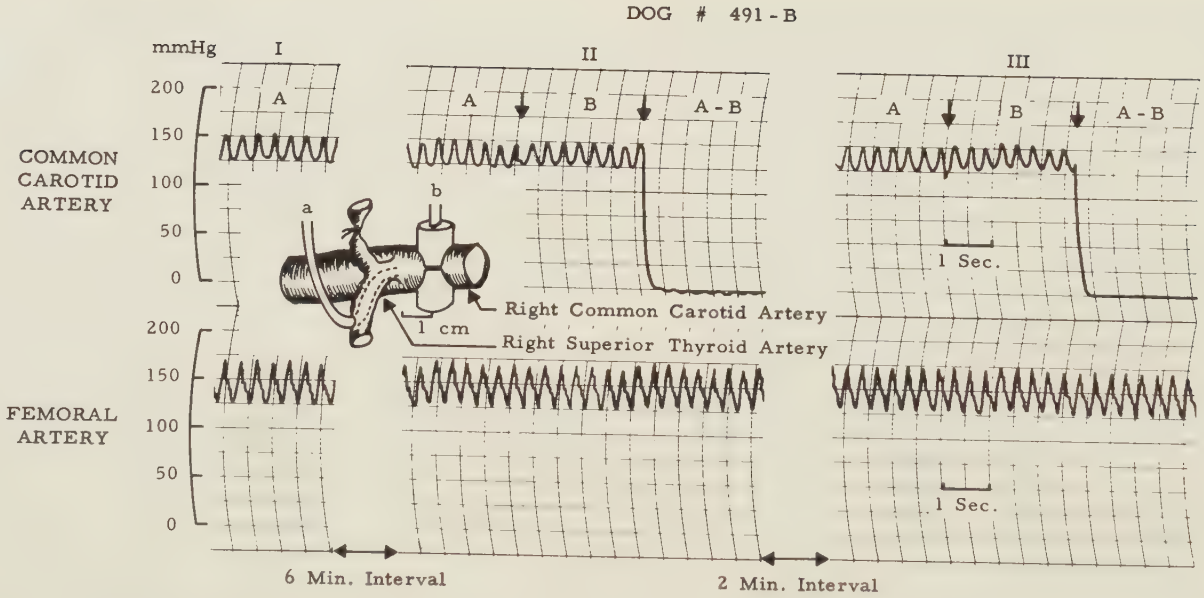

Fig. 3. Comparative measurement of blood pressure with ordinary cannula and external vertical cannula. Upper channel: common carotic artery. A: with ordinary cannula (a), B: with external vertical cannula (b), A-B: differential pressure by mixer. Mixer was switched at arrow. Lower channel: right femoral artery. I: before application of external vertical cannula. II and III: after application of external vertical cannula with connecting tubings 15 cm in length and inside diameters of 0.36 mm and 3 mm, respectively. Reproduced, by permission, from the *Journal of Applied Physiology* 28:702, 1970.

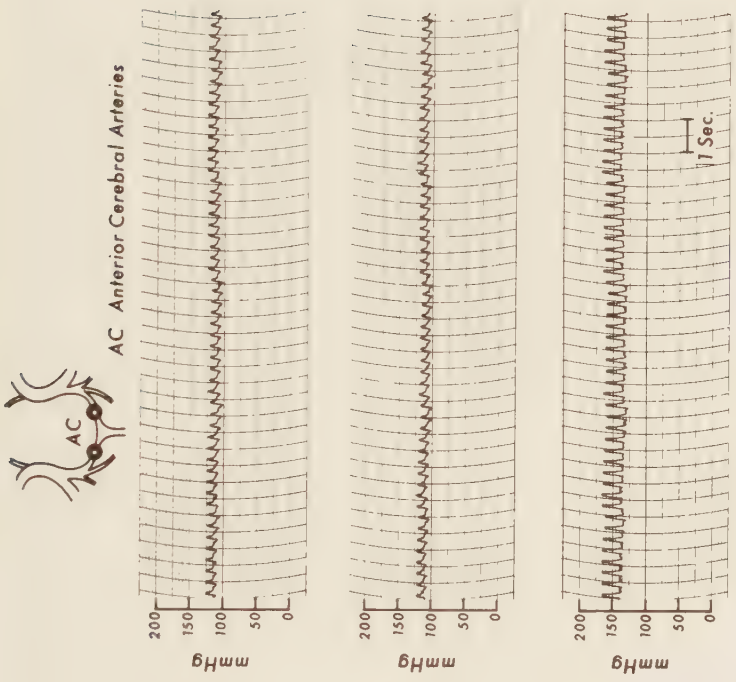

Fig. 4. Blood pressures recorded from right and left anterior cerebral arteries by EV cannulas.

We have found a Tuohy-Borst adapter fitted with a silicone disc (to permit insertion of a needle) satisfactory. For blood pressure tracings, we prefer to heparinize the animal with 5,000 units of heparin; for blood sampling we fill the tubing (connected to the Tuohy-Borst) with heparin before connecting it to the cannula. In drawing blood samples we prefer to withdraw the heparin before the sample is taken, flush the cannula with heparin and saline after the sample is drawn, and then refill the tubing with heparin. This procedure reduces the amount of heparin that goes into the animal and avoids the problem of a possible dilution of the blood. It is our experience that cannulas should be flushed at least once every 24 hours. As in any vascular surgery, the less trauma to the arteries, the fewer the problems of clotting.

Our data are comprised mainly of blood pressure values. After we were satisfied that pressures measured by the usual method of inserting a catheter in a branch and those measured by the use of an EV cannula were comparable (Fig. 3), Dr. Iwabuchi undertook the measurement of pressure in the posterior communicating artery in dog brain (2). Simultaneous measurements of pressure in that artery and in the femoral showed that the mean pressure in the cerebral artery was approximately 82% of that in the femoral artery.

One of us (S.H.) has obtained simultaneous recordings from the right and left anterior cerebral arteries and a femoral artery. The two cerebral arteries differed slightly in both their diameters and their lengths. The pressures were slightly different also (Fig. 4). Whether this difference is significant cannot be judged until we obtain differential pressures. Pressures in the anterior cerebral arteries average 71.1% and 81.9% of the femoral pressure on the right and left sides respectively. Pressures in the anterior communicating arteries are on an average 68.3% of the femoral artery pressure.

SUMMARY

A technique which can be used to cannulate arteries lacking available side branches without interfering with blood flow in the artery has been described. This procedure, termed "external vertical cannulation", has been uniformly successful in studies of blood pressure in arteries comprising the circle of Willis in dogs.

Data comparing pressures in the posterior communicating, the right and left anterior cerebral and the anterior communicating arteries with pressure in the femoral artery are given.

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25. IMPLANTATION OF SOLID STATE PRESSURE TRANSDUCERS

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Selection from the available solid state pressure cells is dictated more by the site of implantation than any other criteria (1, 2). Thus, in this article the techniques that we have used will be described without reference to the size of the transducer (usually 6 mm in diameter); in many instances a smaller size would have been more appropriate but was not used. In this presentation the implantation of the transducers in the left ventricle, left atrium, and thoracic aorta will be described in the order given. It is hoped that a step by step detailed procedure will allow anyone to begin at this point and to devise techniques more suitable than the ones presented.

Prior to use, the pressure cells should be calibrated at or near the body temperature of the animal. After calibration, we have found it very helpful to place a Silastic washer around the back of the head of the transducer. This washer should be a little larger than the transducer. The washer can be held in place by any commercially available cement that is biologically inert. If the transducer is to be used in the thoracic aorta, we normally coat this with some kind of heparin binding agent of which there are several which work equally well. The transducer is then cold sterilized by placing it in solution for 12-24 hours prior to use.

The animal is prepared for sterile surgery and a thoracotomy is made in the left fifth intercostal space. The interspace is opened widely for manipulation of the heart and thoracic aorta.

LEFT VENTRICULAR PLACEMENT

The lungs are removed from over the heart by packing them in a moist towel. The pericardium is incised from the apex of the heart to the atrium. Sutures are placed through the pericardium and anchored to the adjacent muscles or to wound drapes, thus forming a cradle of the pericardium and lifting the heart up slightly. The apex of the heart is lifted out of the cradle and the apical dimple can be easily identified. A suture of 4-0 Tevdek with a

swedged-on needle is used to place a purse string suture around the apical dimple. The purse string suture is started around this point by taking several in and out stitches. The area of the purse string should be large enough to encompass the transducer. The two ends of the suture are tagged for future use and the heart is returned to the pericardium. The pressure transducer is washed in saline to remove the sterilizing medium. If a heparin bonding agent has been used, the transducer is now placed in a cup containing heparin and allowed to set for 2-3 minutes. Following this, the transducer is ready for use. Care should be taken not to wipe across the end of the transducer thus removing some of the bonding medium.

About 1 cm from the end of the transducer, a suture is tied around the cable to use as a marker to ensure that enough of the transducer is placed in the left ventricular cavity. The apex of the heart is lifted out of the pericardium and the surgical assistant takes the two ends of the purse string suture. Using a No. 11 surgical blade, a stab wound is made through the cardiac wall into the ventricular chamber. Very little bleeding should be encountered at this point but if it does occur, the surgeon can put his thumb over the wound. The point of a straight mosquito hemostat is run into the wound and into the left ventricular chamber. As this hemostat is removed it is spread gently to enlarge the wound. At this point bleeding may well occur and if so can again be controlled by the surgeon's thumb or finger being placed over the wound. The shank of the pressure cell is grasped with a straight mosquito hemostat and held gently, insuring that the cell is not damaged. The edge of the cell is inserted into the wound and pushed into the chamber. Great care must be exercised at this point since the pressure cell can be damaged by exerting excessive pressure on it. If the stab wound is not large enough, the mosquito hemostat can again be used to enlarge the opening. After the pressure cell has been pushed into the ventricular chamber, the mosquito hemostat is removed and the assistant should pull the purse string suture tight around the transducer wire (Fig. 1). The transducer is passed into the chamber as far as the marker placed on the lead wire earlier. The assistant finishes tying the purse string suture with multiple knots. Before cutting the ends of the suture it is passed around the transducer wire and tied again. This procedure will hold the transducer in place. If bleeding still occurs around the transducer wire, simple interrupted sutures are used to stop excessive blood loss. The heart is returned to the pericardium.

LEFT ATRIAL PLACEMENT

The left atrial appendage is grasped on one side near its tip with a

Fig. 1. Implantation of solid state pressure cell through left ventricular apex. Heart is being held by a stay suture through adjacent ventricular muscle.

curved mosquito hemostat, and another hemostat is used to grasp the opposite side. The tips of these two hemostats should be facing each other so that bleeding can be controlled. A 2-0 silk suture is passed around both hemostats and looped for future use. The end of the appendage is cut off and a straight mosquito hemostat is passed into the left atrium. The hemostat is spread upon removal from the atrium. The pressure cell is placed in the opening of the atrial appendage and passed into the atrial chamber. Usually this can be done by hand. The suture around the appendage is pulled down and tied. Again the suture is passed around the transducer wire before being cut off. The pericardial sutures are removed and the lungs are unpacked.

AORTIC PLACEMENT

The thoracic aorta is approached by placing a moist towel over the lungs and pushing them toward the right chest. The pleura covering the aorta is incised and a right angle forceps is passed around the aorta. A piece of umbilical tape is pulled around the aorta with the right angle forceps. The intercostal arteries arising from this section of the aorta are identified and ligated until about 10 cm of aorta is clear. All underlying attachments are cut, thus mobilizing this segment. The pressure cell that will be used for this implant should have a heparin bonding agent applied to its surface. At this point the transducer can be soaked in heparin. The aorta is occluded at both ends of the segment by either using vascular clamps or umbilical tape pulled through pieces of rubber tubing. Following the occlusion the artery is incised using a No. 11 blade. The opening is enlarged just enough to pass the transducer. After placing the transducer in the lumen of the vessel, 4-0 Tevdek is used to sew up the arteriotomy. After suturing the vessel wall, a second suture line is made using the adventitia of the aorta. The distal occluder is released and then the proximal occluder is relieved gradually. If excessive bleeding occurs, single stitches are used to stop the bleeding. The wire from the transducer should be held firmly at this point to prevent the transducer from being washed downstream. A silk suture is tied around the transducer wire as close to the aortic wall as possible. Usually this will insure that the cell is not pulled downstream. A length of Dacron graft material of appropriate size is cut longitudinally and slipped around the vessel at the site of implant. The graft is next cut slightly in the circular direction and slipped around the transducer wire. The ends of the graft are sewed together both in the circular and longitudinal direction. This graft should fit snugly around the vessel without constricting it. The wire from the transducer is run dorsally along the rib cage and anchored with a suture

near the aorta. This suture and the graft prevent the transducer from being pulled out inadvertently and from backing out of the aorta respectively.

OVERALL RESULTS

We have not had any difficulty with implants in the left ventricle, right ventricle, left atrium, or right atrium for many months at a time if the above procedures are followed. The greatest difficulty arises with aortic placement of the pressure cells. Care must be exercised and the Dacron graft is a necessity. If the precautions described above are followed, we again have not encountered any major obstacles. Emboli and clots may develop from or on the aortic transducer, and a heparin bonding material should be used on this pressure cell. The incision is closed in the usual manner, making sure that a small loop of transducer wire is left in the chest cavity.

SUMMARY

The implantation of pressure cells in the various chambers of the heart has been accomplished in many animals without any evident embolic accidents. Generally, these implantations were accomplished without any heparin-bonding procedures to retard the formation of streaming clots over the pressure transducer. A patch of Dacron graft material has been found necessary for prevention of arterial wall erosion and to insure retention of the pressure cell in the artery. By following these few simple techniques, solid state pressure cells can be implanted easily in any part of the organism.

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26. BLOOD PRESSURE MEASUREMENT WITH CHRONICALLY IMPLANTED, INTRAVASCULAR TRANSDUCERS

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INTRODUCTION

One of the primary foci of this laboratory is the design, fabrication, and testing, in actual physiological experiments, of instrumentation systems which are capable of recording blood pressures for periods of up to at least 45 days, unattended and maintenance-free, without interference with normal organ functions. A bioinstrumentation system of this nature allows utilization of unrestrained subjects in a variety of experimental situations closely resembling the physiological and possibly the psychological norms of the subjects. Additional reasons for employing an implantable blood pressure sensor and signal conditioning electronics are the reliability of the implanted sensor signal in repetitive recording sessions, and the feasibility of chronic or long term studies without the trauma of repeated catheterization procedures and their accompanying physiological and psychological aberrations.

CHARACTERISTICS OF BLOOD PRESSURE SENSORS

The sensing of blood pressure in all of our experiments was accomplished by the use of implanted intravascular diaphragm-actuated pressure gauges (Konigsberg Instruments). These gauges are available in a variety of sizes, and the ones employed in our laboratory are in the 4.0 mm to 6.5 mm diameter range. This type of gauge was selected for several reasons. The gauge body is of unalloyed titanium which is highly corrosion-resistant, allowing long term direct contact with body fluids. The transducer sensitivity is approximately 30 mv per 300 mm Hg when used as suggested by the manufacturer, which is satisfactory for our application. The frequency

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response of the sensor is well in excess of that required to obtain dynamic blood pressure, and the gauge temperature characteristics can be determined and dealt with readily. The baseline and sensitivity characteristics are also predictable and adjustments can be made to compensate for changes in these parameters. Finally, one of the more important factors is that the sensor is applicable to low current operation. This final consideration in conjunction with the previously mentioned small size and good temperature stability and the promise of acceptable time stability formed the criteria for choice of the Konigsberg Instruments gauges. (1)

SURGICAL PROCEDURE

Prior to implantation of a blood pressure sensor, the blood vessel diameter is estimated, and based upon this information, a transducer is selected which will not impede the blood flow appreciably once it is in place. Recording blood pressure from the abdominal aorta in 30-50 pound dogs invariably required a 5 mm diameter transducer, while a diameter of 6.5 mm was satisfactory for 60-80 pound dogs. Recording from the thoracic aorta in 30-50 pound California sea lions was accomplished by using a 6.5 mm diameter gauge, as was recording blood pressure from the thoracic inferior vena cava in 50-125 pound sea lions.

Preparation for implantation consisted of sterilization of the sensor in a mixture of 50% aqueous zephiran chloride and 50% ethanol for 24 hours prior to surgery. The animal was then prepared for surgery and given a general anesthetic, usually halothane (2-bromo-2-chloro-1,1,1-trifluorethane) vaporized with oxygen. All operations utilized usual sterile procedures to minimize the possible complication of infection in the post-surgical recovery period. The vessel to receive the implant was exposed and two lengths of cotton umbilical tape were placed around the vessel, one proximal and one distal to the implant site. The cotton umbilical tape was used to alleviate the problem of intimal damage as a result of clamping with a vascular clamp. Retraction on the umbilical tape was then used to arrest the flow of blood in the segment between the ligatures, and a small longitudinal incision approximately 7-10 mm in length was made through the vessel wall into the lumen. The transducer head was then "buttoned" into the incision and the incision was closed around the transducer cable with a fine (4-0) Mersilene suture to prevent hemorrhage. A section of Dacron arterial graft approximately 1.5 cm by 2.0 cm in size was then sutured to the adventitia of the blood vessel over the incision site with the cable emerging from the center of the Dacron patch. The Dacron provided structural integrity to the vessel wall at the implant site, thus reducing the possibility of vessel rupture or the formation of an aneurysm at the site due

to vessel wall weakness.

The transducer cable was then coiled in a 3 cm diameter "strain loop" and sutured to the pleura and overlying muscles in the case of thoracic implants, or to the peritoneum and overlying muscles in the case of abdominal implants. This was done to reduce the strain on the blood vessel itself. The cable was then connected to an implantable telemetry package which was sutured in place, or led out adjacent to the incision and coiled in a subcutaneous pocket for exteriorization at a later date.

CALIBRATION PROCEDURE

Periodic pressure calibration was made to quantify the data obtained. This was accomplished by anesthetizing the experimental subject and performing a catheterization via a cutdown. An external, previously calibrated blood pressure transducer was attached to a catheter, and the catheter was then advanced until the catheter tip reached the level in the blood vessel adjacent to the implanted sensor. In the case of the arterial blood pressure sensor implants, the catheterization was done through the femoral artery. The venous pressure calibration was done through the iliac vein. The two pressure recordings were then displayed simultaneously on a two-channel strip chart recorder (Brush Mark 280). The known systolic and diastolic pressure readings from the external pressure gauge recording were charted against voltage readings produced at corresponding pressure points by the implanted pressure gauge channel. This provided a calibration in mm Hg/volt which was used as the calibration in subsequent data recording sessions.

The stability of the transducer sensitivity and the accompanying circuitry was felt to warrant performing the calibration procedure approximately every 30 days to assure accurate, long term quantitative information. The monthly calibration procedure was found to be relatively atraumatic, and if carefully repaired, a femoral artery could be catheterized 5-10 times without the development of a stricture. The significance of this finding lies in the fact that if one were to catheterize both femoral arteries alternately, a calibration could be done every 30 days for more than a year. This procedure thus affords a reliable method of calibration for long term studies employing chronically implanted instrumentation.

MODIFICATION OF THE IMPLANTABLE INTRAVASCULAR PRESSURE TRANSDUCER

The problems encountered in measuring small changes in blood pressure while the experimental subject was exposed to large changes in ambient

pressure were solved by modifying the intravascular pressure transducer discussed above. These problems were encountered while measuring blood pressures in free-swimming trained sea lions who were diving voluntarily to depths of up to 6 meters and thus experienced fluctuating ambient pressures of approximately 500 mm Hg. The transducer was modified to accept a small diameter Silastic tube which vented the back of the gauge to ambient pressure (Konigsberg Instrument P20G) (2). Figure 1 illustrates the transducer cable configuration with a Luer-Lok fitting attached to the

Fig. 1. Implantable pressure transducer illustrating modification for use in changing ambient pressure environments.

reference tube. This tube was brought out through the skin of the experimental subject and connected to an air-filled external pressure reference bulb mounted on the data recording device which was carried by the experimental subject. The bulb and pneumatic tube constituted a closed volume and fluctuations in ambient pressure were thus conducted to the back of the gauge diaphragm to nullify the ambient pressure change influence upon the face of the gauge diaphragm.

BLOOD PRESSURE SENSOR APPLICATIONS

Until recently most studies involving the measurement of cardiovascular parameters have of necessity been made under static conditions in anesthetized or restrained subjects. A comprehensive review of the available methods for measuring blood pressure chronically in unanesthetized dogs was presented by Wilhelmj and McMarthy in a recent text (3) in which the many difficulties associated with the auscultatory and direct catheter techniques were clearly presented.

The need for more information about dynamic changes in blood pressure is becoming increasingly evident in physiological research. The major contribution of miniature implantable intravascular pressure transducers has been to free the investigator from the constraints of earlier methods and to allow him to examine blood pressure under more physiologically "normal" conditions in free-roaming, unanesthetized animals. Experimentation in this laboratory employing implantable transducers has been conducted in three general areas: emotional stress induced by either obedience training or territorial defense (4, 5); physical stress induced by treadmill and long distance running (4, 5) or free-diving in the case of marine mammals (6); and modification of the blood pressure control system by drug application (7). In all cases, blood pressure has been obtained by the placement of implantable sensors in either the aorta or the vena cava in male mongrel dogs of German shepherd descent and in California sea lions.

1. *Emotional Stress-Obedience Training*

This study employed male mongrel dogs of German shepherd breeding, weighing approximately 50 pounds. A 6.5 mm diameter intravascular pressure transducer was implanted in the abdominal aorta below the bifurcation of the renal arteries. The transducer cable was exteriorized and attached to a transmitter and signal conditioning package carried in a nylon mesh jacket worn by the dog (8, 9).

It was hypothesized that "obedience training" would be as psycholog-

ically stressful and novel to a dog as, for example, astronaut training would be to a man. Hence the initial and most of the following recording sessions were made with the animal wearing a standard chain training collar attached to a 6-foot leather training leash. The dog was primarily handled by the same individual who trained the animal according to obedience training procedures set forth by the Air Force (10) and by popular books on dog training. The dog was taught to "heel", lead by leash, "sit," automatic sit on stop, "stay," "come," and "stand" on command. The only punishment rendered was a sharp pull on the training collar; the only reward was petting and verbal praise. Verbal commands were given only once.

The highest blood pressures recorded were during obedience training when a given command was new to the dog, and following correction for mistakes. At these times systolic pressures in excess of 245 mm Hg were recorded. As training progressed and the animal became familiar with the commands, the blood pressure response to the commands became less until he executed the commands with little or no blood pressure elevation.

2. *Emotional Stress-Territorial Intrusion Studies*

In this study territorial intrusion was employed as a situational stress to study the blood pressure response. Two male dogs were allowed on separate occasions to spend a period of time in an area in order to develop a territorial defense response. At the completion of the acclimatization period, an intruder animal was allowed to enter while the test animal's response was observed. This was performed in both acute and subacute (24-hour) intrusion experiences.

The response of one of the animals was quite strong in the acute phase, which was made evident by the aggressive nature of the test animal and the increases in both blood pressure and heart rate. The blood pressure response can be seen in Figure 2. The second animal was relatively unresponsive to the acute intrusion. In the subacute (24-hour) intrusion both test animals demonstrated a significant response by blood pressure and heart rate increases while sleeping. There appeared to be discrimination among animals as to the degree of threat posed by an intruder animal in that one dog was unresponsive to one intruder and markedly responsive to another.

3. Physical Stress-Exercise Studies

Graded treadmill exercise was used to examine the effects of extreme physical stress upon arterial blood pressure. A total of 28 runs at various speeds and inclines on a treadmill were performed. The results from these

graded treadmill studies suggest that heart rate mirrors metabolic demands and not necessarily emotional arousal. Heart rates of 300 beats per minute were not uncommon at the higher work loads. The increase in heart rate correlated well with increases in work load, whereas blood pressure tended to remain unchanged or slightly increased. Blood pressure responses were

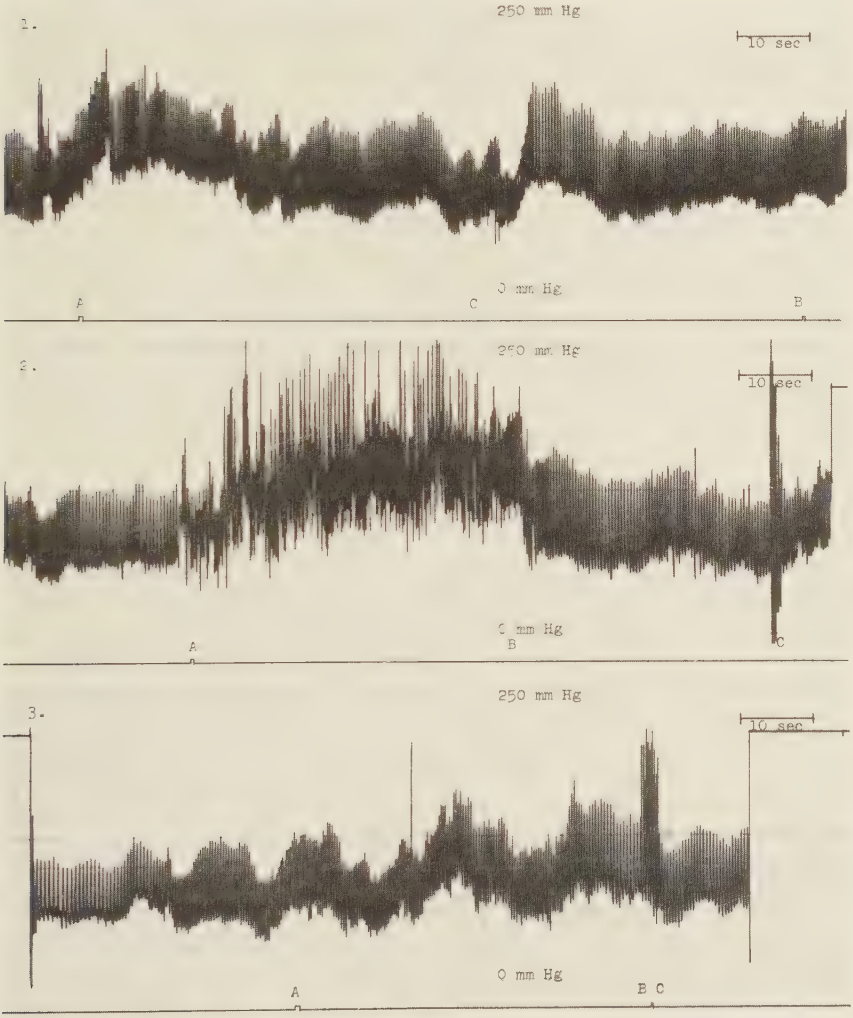

Fig. 2. Acute intrusion recordings of dog #215. (1) Day 1, control encounter; no territorial identification. (2) Typical intrusion. (3) Typical neutral encounter. (A-intruder enters; B-intruder exits; C-test animal shaking.)

found to change radically with training and the elimination of emotional factors associated with the treadmill task.

4. Physical Stress-Breath-Hold Diving Studies

In these studies central venous blood pressure was recorded in free-swimming trained California sea lions diving in the ocean in an attempt to elucidate the cardiovascular adjustments made during breath-hold diving. The ambient pressure compensated transducer was implanted in the inferior vena cava approximately 5 cm caudal to the right atrium of the heart in 80-125 pound sea lions.

After an initial rapid elevation in central venous pressure of some 4.8 mm Hg, the pressure returned to a steady value of 1.5 to 2.0 mm Hg above the predive level. When the animal surfaced, the central venous pressure returned to control. The apparent absence of thoracic vascular engorgement during swimming and diving periods, as indicated by only a slight increase in overall central venous pressure throughout the dive, suggested the operation of some highly sensitive regulatory mechanism to meter the flow of blood into the thoracic circulation. The inferior vena caval sphincter is an anatomical entity capable of exercising this regulatory function.

5. *Drug Studies*

The purpose of this study was to investigate the role of circulating catecholamines in the cardiovascular response to exercise. The drug selected for this study was phenoxybenzamine because of its specificity in blocking the alpha adrenergic receptors.

Four phenoxybenzamine treadmill runs were completed on each test subject. Each animal received phenoxybenzamine in a dose of 1 mg/kg of body weight prior to the run. The well diluted (1:50) drug was administered by intravenous injections over approximately a 5-minute period. No anesthetic agents were employed, but attempts were made to keep the animal as quiet as possible during injection. Time elapsing from completion of the phenoxybenzamine injection to the commencement of the treadmill run varied between 30 minutes and 90 minutes.

Six control runs and four runs after phenoxybenzamine injections were completed on all animals. The subjects were given several familiarization runs on the treadmill before recordings were made. A "hot shot" shocking device was used to encourage participation on the tests. The handler stood in front of the treadmill holding the animal with a leash attached to a choke chain around the dog's neck. This procedure coupled with the presence of

an assistant using the shocking device at the rear of the treadmill enabled the handler to maintain control of the animal and prevented the subject from drifting toward the rear of the treadmill during the more strenuous phases of the exercise test.

During the control runs blood pressures could not be correlated with increased work loads (Fig. 3). The heart rates of all test subjects tended to increase in a linear fashion as the work load increased. The findings support the conclusion made in the exercise studies that during exercise, increased work loads are reflected by increased heart rates, while the blood pressure

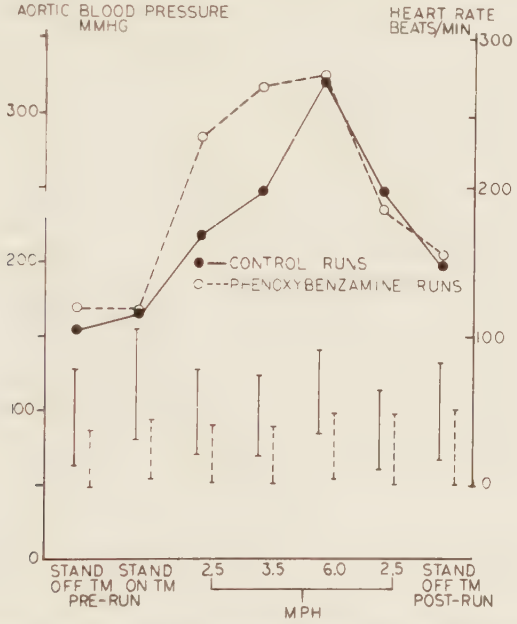

Fig. 3. Blood pressure and heart rate responses to graded treadmill exercise of control and phenoxybenzamine infused animals.

responses were variable.

During the exercise phase of the phenoxybenzamine runs of all dogs, both systolic and diastolic pressures decreased significantly when compared with control blood pressures. These blood pressure decreases were seen with higher heart rates attained during the phenoxybenzamine runs.

SUMMARY

The inherent disadvantages of other methods used to measure blood pressures and heart rates in unrestrained animals have been reviewed; and it

is obvious that they add to the complexity of separating psychological factors from the physiological parameters under investigation. This is not to deny that cortical influences may be intimately involved in most physiological reactions, but if the response is to be quantified, the psychic variable must be controlled. If the effects of social interaction and behavior on cardiovascular dynamics are to be thoroughly investigated, telemetry offers a new and improved approach.

The miniaturized system used in these studies eliminates clouding of the data by emotional responses which occur in animals with other procedures and permits a more valid interpretation of the influence of the manipulated variable on physiological function. The method also allows for a better definition of physiological baseline conditions. The view that the animal may never grow completely accustomed to attachments has been discussed by several recent investigators. The advantages of using remote recording in studies which demand complete relaxation and freedom of the animal are evident.

This method permits the necessary latitude for investigating the cardiovascular responses under broad environmental conditions. The technique as described appears to have widespread application in chronic studies. It is apparent, therefore, that the collection of quantitative and qualitative blood pressure data on free-roaming animals is now conceivable with the use of telemetry techniques. The only limitations of the method include the delay for recovery following surgical implantation and the initial cost and availability of the required technical apparatus.

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27. IMPLANTATION OF ELECTROMAGNETIC FLOW PROBES ACROSS CARDIAC VALVES IN DOGS

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Phasic flow through normal and prosthetic mitral valves has been described (1-3) using an electromagnetic flow probe placed above the mitral valve in the left atrium. Using this technique the rate of change of flow could then be examined during each part of the cardiac cycle. Mitral and tricuspid flow obtained simultaneously with ventricular volume or ventricular dimension measurements would add valuable new information. Ventricular filling may also be compared with ventricular pressure measurements, using a chronically implanted catheter (4). In addition, catheters may be chronically implanted in the left atrium and left ventricle and data concerning pressure gradients could be obtained simultaneously. This technique may also be applied to the tricuspid valve, with a slight change in probe construction.

CONSTRUCTION AND IMPLANTATION OF A FLOWPROBE ABOVE THE NORMAL MITRAL VALVE

Circular flow probes are constructed using a technique previously described (3, 5). The probe is constructed with inside diameters from 20 to 25 mm for implantation in dogs weighing 45-60 pounds. The ratio of inside diameter to outside diameter is kept as small as possible when constructing intracardiac probes to avoid producing a stenosis of the valve orifice.

As the probe will be in the blood stream continually it is necessary to use a very low moisture absorbing material for encapsulation. Epoxy resin No. 0151 (Hysol Corporation) has a water absorption of 0.37 per cent when immersed for 24 hours. The volume resistivity is 1.0×10^{14} ohm/cm at 77° F. This material has also been found to be nonreactive when in the blood stream for up to two months (3).

The electrical operation of the intracardiac probe is similar to extravascular probes. However, as the probe actually measures the velocity of blood flow, it is necessary to position the probe in the atrium so that the blood flows through the probe as uniformly as possible. It is also necessary to keep the probe electrodes 2 or 3 mm away from the valve leaflets. If the leaflets are allowed to come between the probe electrodes an artifact is produced (3). A completed probe which has been covered with Dacron cloth to provide a sewing ring is shown in Figure 1. The inside diameter is 22 mm and the outside diameter is 34 mm.

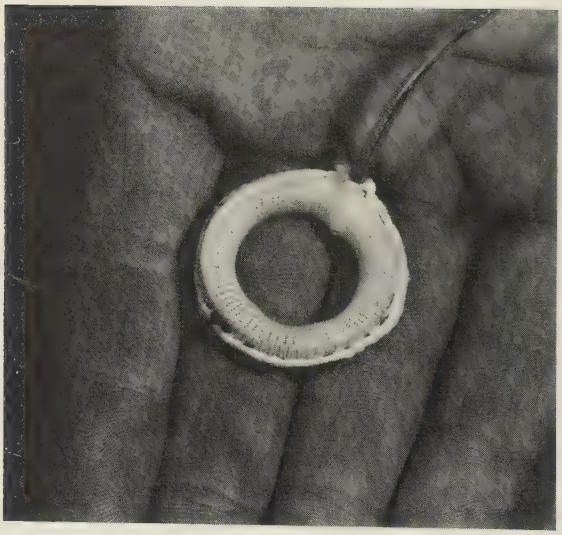

Fig. 1. Dacron covered circular flow probe for chronic implantation in the left atrium above a normal mitral valve.

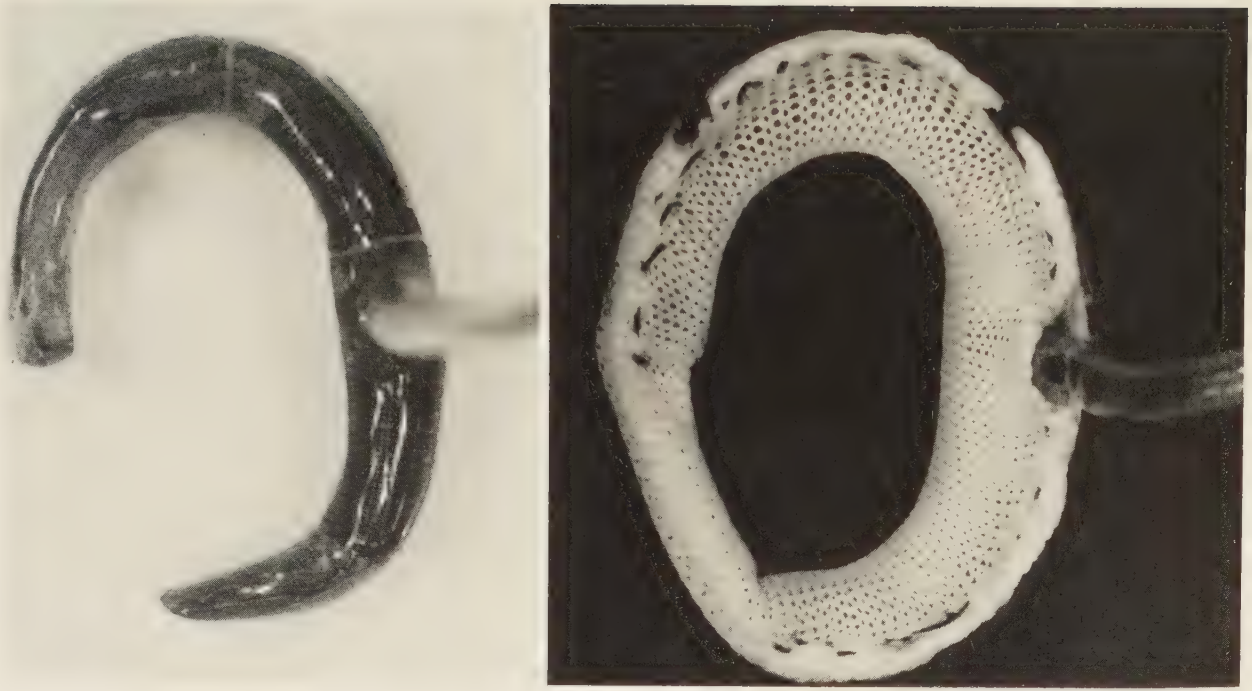

Fig. 2. On the left is an elliptical probe for implantation in the right atrium above a normal tricuspid valve. The open space is positioned over the location of the conduction system. On the right is the same probe, covered with Dacron cloth, ready to be sutured into the right atrium.

SURGICAL PROCEDURE FOR MITRAL PLACEMENT OF A FLOW-PROBE

The probe is gas sterilized prior to surgery. The chest is entered on the left side through the fourth intercostal space. The right atrial appendage is cannulated for the venous inflow to the cardiopulmonary bypass, and the arterial return is provided via the carotid artery. After bypass is established, an indwelling catheter (4) is implanted in the left ventricle through a stab wound in the left ventricular apex. The catheter is held in place with a purse string suture and pledgets. This catheter is used during the bypass to provide decompression of the left ventricle and later will be used as a chronic left ventricular catheter for pressure measurement. The heart is fibrillated with AC current.

A left atriotomy provides exposure of the mitral valve. The flow probe is sutured in the left atrium just above the mitral valve using eight equally spaced mattress sutures of 2-0 Tevdek. Care must be taken in placing sutures in the lateral atrial wall, as they will be placed just above the coronary artery in the A-V groove. After the probe is in place the flowmeter cable is brought out through the atriotomy, and the atrium is closed with a running mattress suture which seals the atrium around the probe cable. The air is expelled prior to placing the last suture in the atriotomy. A second indwelling catheter (4) is placed through a stab wound in the left atrium and held in place with a purse string suture. These two catheters may then be used to measure changes in left atrial and left ventricular pressures.

After the heart is defibrillated, the bypass is discontinued and the flowmeter cable and two catheter connectors are brought out through the thoracotomy. Then they are tunneled under the skin to the dorsal midline where they are exteriorized. The chest is closed in the usual fashion and the animal allowed to recover. The dogs are given 300 U/Kg of Heparin subcutaneously every 12 hours to prevent clotting on the flowmeter probe.

MODIFIED CONSTRUCTION OF AN INTRACARDIAC FLOWPROBE FOR IMPLANTATION ABOVE THE TRICUSPID VALVE.

The construction technique for tricuspid flow probes is altered slightly because of the anatomy of the right atrium (6). The tricuspid orifice is not round but is slightly concave-convex, with the right atrium above the valve appearing as an ellipse. It has been shown that a round probe placed in the right atrium will distort the tricuspid valve and pressure on the septum with its underlying conduction system will produce conduction abnormalities (6). Therefore the probe is made in the shape of an ellipse with a ratio of

major to minor axis of 1.3/1. A 50 pound dog would require probes with an approximate inside diameter of 20 mm by 15 mm. In addition, the probe is constructed with an open space as shown in Figure 2A. This open space is positioned over the conduction system and avoids the possibility of pressing on the bundle and producing conduction abnormalities. Figure 2B shows the probe covered with Dacron cloth to provide a sewing ring.

SURGICAL PROCEDURE FOR TRICUSPID PLACEMENT OF A FLOW-PROBE

The chest is entered from the right side through the fourth intercostal space. The azygos vein is ligated. A purse string suture is placed in the wall of the right atrium near the inferior vena cava (IVC) and a cannula is placed through a stab wound with its tip in the IVC. A similar cannula is placed through the right atrial appendage with the tip in the superior vena cava. This cannula is held in place with a purse string suture around the atrial appendage. These two cannulae will provide the venous inflow to the cardiopulmonary bypass. A piece of umbilical tape passed loosely around each of the cavae can be drawn tight later, after bypass has been established, to prevent blood from entering the right atrium. The arterial return from the bypass enters a cannula placed in the carotid artery. After bypass is established, the right atrium is opened and a suction tip is placed in the coronary sinus. The right atrium should then be relatively free of blood and there should be adequate exposure of the tricuspid valve.

The tricuspid style electromagnetic flow probe is then sutured in place with eight equally spaced 2-0 Tevdek sutures. No sutures are placed near the open space provided in the flow probe, which is placed directly over the AV node and bundle area. Care must be taken not to obstruct the outflow of the coronary sinus. After the flow probe is sutured in place, with the heart beating, the right ventricle is filled with saline and proper closure of the tricuspid leaflets is verified. Cardiopulmonary bypass is discontinued after closing the atriotomy with a running mattress suture, which seals the atrium around the flow probe cable.

An indwelling catheter (4) is placed in the right ventricle through an apical stab wound and held in place with a purse string suture. A similiar catheter is placed in the right atrium through a stab wound in the atrial appendage. The flow probe cable and catheters are exteriorized in the same manner as for mitral probe implant. The chest is closed in the usual fashion.

PHASIC MITRAL FLOW PROFILE

An example of phasic mitral flow is shown in Figure 3. Left atrial and

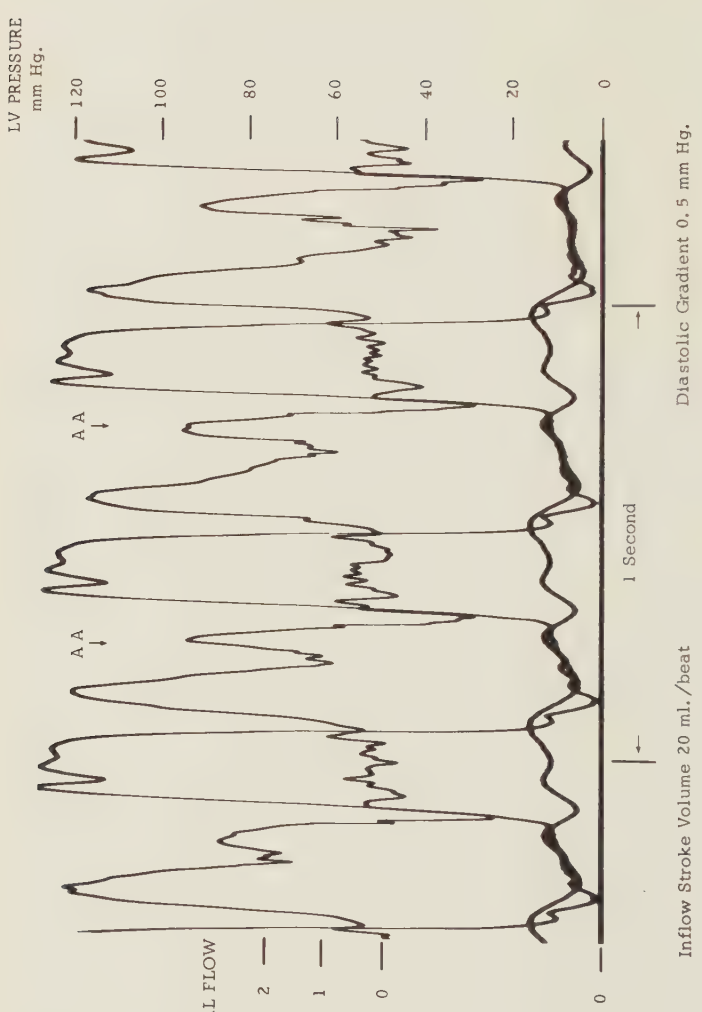

Fig. 3. **Phasic mitral flow and left atrial and left ventricular pressure recorded in a chronic unanesthetized dog.** Mitral flow in L/min. Reproduced, by permission, from the *Journal of Thoracic and Cardiovascular Surgery* 61:235, 1971.

left ventricular pressures were recorded on equisensitive Statham P-23 strain gauges using the two indwelling catheters. The flow was measured using a Medicon K2000 gated sine wave electromagnetic flowmeter, and the flow and both pressures were recorded on a Sanborn 150 photographic recorder. The effect of atrial contraction on mitral inflow is shown in Figure 3 at the points marked AA.

It should be noted that mitral inflow does not cease at the instant of reversal of the left atrial to left ventricular pressure gradient. This is thought to be due to the inertia of the blood as it rushes into the ventricle. The blood is under deceleration and its forward flow into the ventricle is stopped within a few milliseconds by the reverse atrioventricular gradient. At this point the mitral flow record shows a negative spike caused by the closed mitral valve billowing back into the atrium, and represents the compliance of the valve (2). The inertial effect is less significant at slow heart rates, as ventricular filling is essentially complete, and mitral flow velocity is reduced prior to the onset of the next ventricular contraction. However at high heart rates, mitral flow velocity is high when the atrioventricular pressure gradient reverses, and therefore the inertial effect is greater. This results in mitral valve closure occurring significantly after atrioventricular pressure gradient reversal.

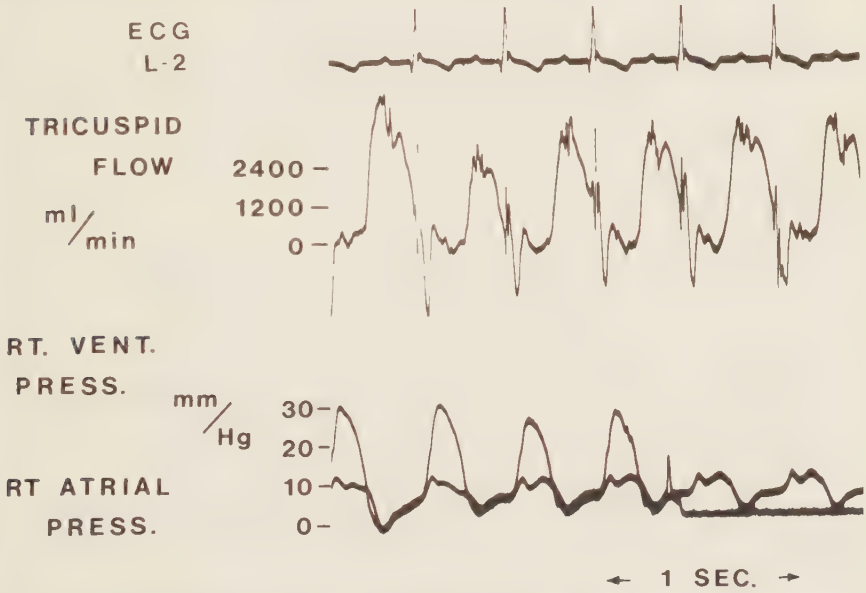

Fig. 4. Phasic flow through a normal tricuspid valve, right atrial and right ventricular pressures, and electrocardiogram (lead II), showing normal sinus rhythm.

PHASIC TRICUSPID FLOW PROFILE

An example of the phasic tricuspid flow profile is shown in Figure 4. The use of an elliptical probe with an open space over the conduction system permits one to obtain a normal sinus rhythm (6). It should be noted that the onset of tricuspid flow and therefore right ventricular filling coincides well with the reversal of the atrioventricular pressures. The tricuspid valve closes and right ventricular inflow ceases a few milliseconds after the instant that the right ventricular pressure exceeds right atrial. This suggests an inertial effect in right ventricular filling similar to that seen in the mitral flow record. The right atrial component of tricuspid flow appears to be less significant than that of the left atrium on mitral inflow. There is an ECG artifact on the flow record which is due to the close proximity of the probe to the depolarizing myocardium.

SUMMARY

Electromagnetic flow probes may be constructed for intracardiac placement above the mitral and tricuspid valves in dogs. With the use of cardiopulmonary bypass, direct vision may be employed to suture these flow probes in the atria above the atrioventricular valves. If a probe of proper size is chosen, there should be no significant diastolic gradient and the probe should not produce any valvular insufficiency. Catheters may be implanted on either side of the valve and pressure-flow characteristics may be examined.

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28. IMPLANTATION OF FLOW TRANSDUCERS ON THE LEFT CORONARY ARTERY AND CENTRAL AORTA

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During the past several years, a good share of our effort has been directed to the study of the coronary circulation in the unanesthetized dog.[1] This required, among other things, the implantation of flow transducers on the coronary arteries, particularly the left, and on the ascending aorta. The present report deals with the implantation technique. The surgical approach and procedure have been described previously and will be treated very briefly; emphasis will be on details which we believe helpful toward achieving a good preparation.

LEFT CORONARY ARTERY.

Our first attempts were measurement of total left coronary artery inflow by placing a transducer on the main left coronary artery. A report of this early work was presented in 1960 (1). Here, stabilization of the transducer presents no problem since it is firmly supported in a groove by the short vessel and the surrounding structures. Mechanical flow zero was obtained by placing occlusive devices on both the circumflex and descending branches near their origin, and correcting for septal artery flow (2).

However, the main left coronary artery of the dog is extremely short and only 1 out of 3 or 4 is suitable for such measurement. Because of these anatomical limitations, most measurements of flow in the left coronary artery are now made on either the descending or the circumflex branch (3), and occasionally on both simultaneously (4). The transducer implantation procedure is basically the same for either branch, and only installation on the circumflex will be treated.

[1] In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

The chest is usually entered by the fifth left intercostal space because this route is also favorable to the implantation of other devices required by our experiments. The left phrenic nerve is dissected free from the pericardium, which is then opened along a line parallel and slightly anterior to the course of the left circumflex branch. The circumflex is dissected free of fat and surrounding tissues for 1 cm of its length, near its origin. A flow transducer and a zero cuff (5) are then applied to the vessel.

Particular attention is given to the "fit" of the transducer on the vessel, to the orientation and stabilization of the transducer and cuff, and to the routing of the transducer cable and cuff inflating tube. The artery diameter is measured with calipers. Since transducers are available in 0.5 mm size increments, a transducer is chosen such that its lumen either matches the vessel diameter, or is smaller by 0.4 mm or less. A strip of Ivalon sponge (Unipoint Laboratory, P. O. Box 268, High Point, N. C.), 2 to 3 mm across, is placed between the transducer and the cuff, encircling the vessel, and serves to keep them apart. The pericardium is then repaired loosely with interrupted stitches. The transducer and occlusion cuff are carefully oriented and aligned on the vessel, and are stabilized by attaching the cable and inflating tube to the pericardium, leaving ample slack or safety loops (Fig. 1). Whenever the experiment necessitates the removal of the pericardium, the cables are attached to the epicardium.

ASCENDING AORTA.

The ascending aorta is cleared of all fat and extravascular tissue for a length of about 2 cm, and a transducer of appropriate size installed. Proper orientation and stabilization of the transducer are assured by the stout and rigid aorta. The transducer cable is led out along the mediastinum, as shown in Figure 1. Aortic ruptures, a discouraging problem at first, have essentially been eliminated (no rupture in the last 27 dogs) by careful attention to transducer design, transducer "fit" on the vessel, and the placement of a ring of Ivalon sponge on the proximal side of the transducer.

Soon after the chest is opened, the aorta is dissected and measured with calipers. A transducer is chosen with a lumen diameter larger by 1 to 2 mm than the measured diameter of the aorta. The "fit" appears very loose, and often it is not possible to record a good signal at this time. A strip of Ivalon sponge, 5 to 6 mm across, and of a length (unstretched) equal to 90% of the transducer circumference, is placed as a ring around the aorta, on the proximal side of the flow probe. This Ivalon ring prevents the aorta from impinging on the proximal edge of the transducer with each heart beat.

The transducer used must be of low mass and occupy minimal space

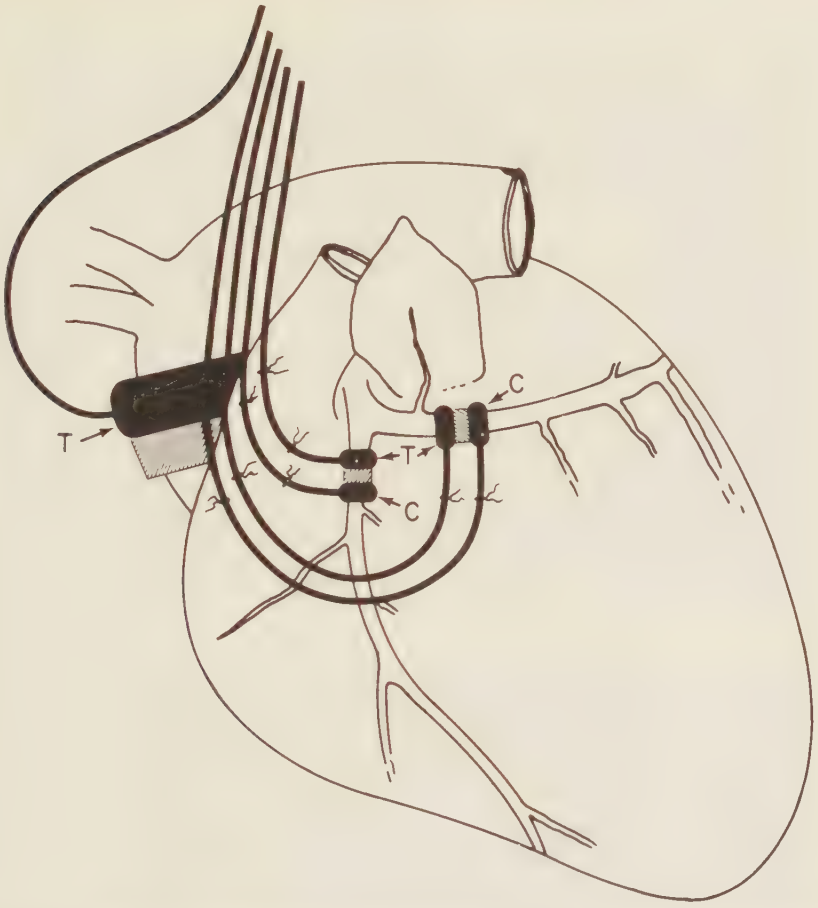

Fig. 1. Schematic representation of the preparation. T: flow transducers; C: occlusive cuffs; cross-hatched areas: Ivalon sponge. Transducers and zero cuffs are oriented and stabilized with ligatures as shown. The left atrial appendage is retracted for clarity.

along the vessel axis. Except for minor mechanical and electrical modifications, it is similar to that described previously (6). Figure 2 shows a 27 mm lumen diameter transducer. The iron core design (left) is used because it makes possible a transducer of very small width. The finished unit (right) weighs 13.5 grams, excluding cable and connector, and is only 10 to 11 mm wide (length of vessel occupied).

Although the transducers seem to be rather loosely fitted to the vessels,

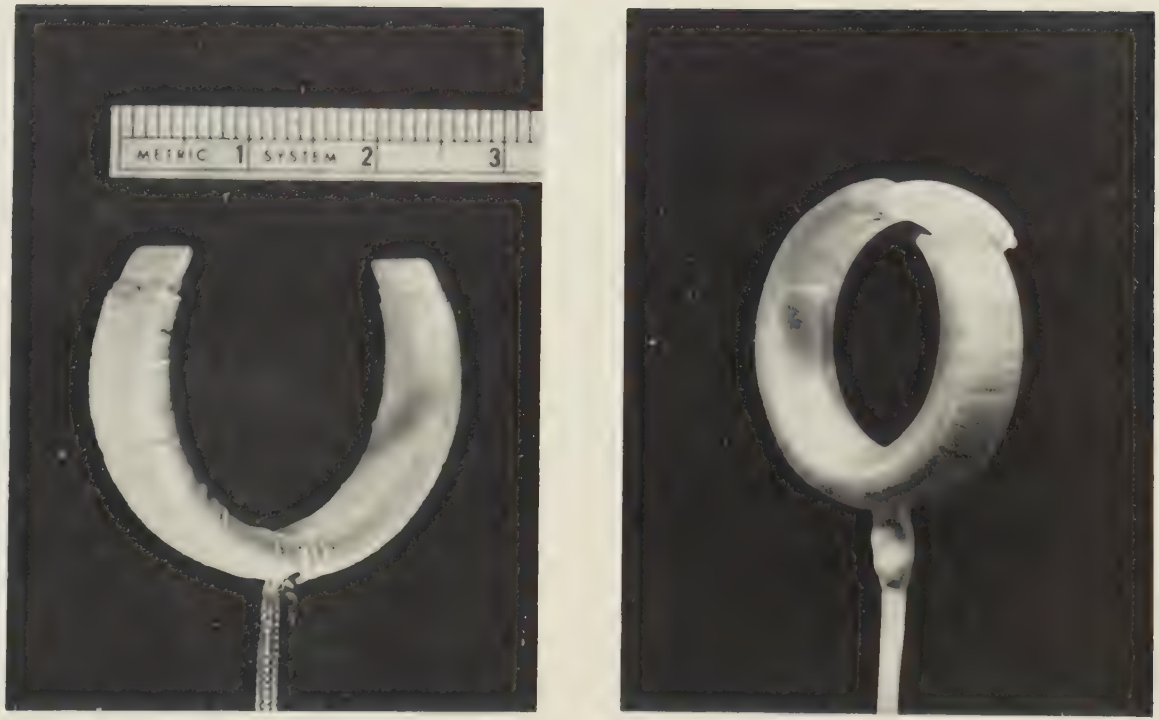

Fig. 2. A flow transducer of 27 mm lumen diameter. Left: iron core dimensions: 30 mm I.D., 33.75 mm O.D., 7.25 mm wide, 25 mm gap. The O.D. tapers inward toward the gap. The coil consisting of 2 layers (190 to 200 turns) of No. 32 wire, is excited at 0.3 Ampere. Right: the finished unit (shutter partially inserted) weighs 13.5 grams, excluding connector and cable, and is only 10 to 11 mm wide.

acceptable recordings are generally possible the day after surgery; good traces are obtained even under severe conditions such as exercise (7), by the time the animal recovers from surgery (10 to 14 days). Because our experimental design requires the placement of indwelling catheters in the left coronary artery branches, large dogs (22 to 30 kg) are generally used. They are usually eager to please, very amenable to training, quite sturdy, and they recover rapidly from surgery. However, we have occasionally used small dogs without difficulty.

Figure 3 shows a typical recording of simultaneously measured left descending coronary flow, left circumflex coronary flow, and cardiac output, obtained 27 days after surgery. Also shown for the left descending coronary flow is a mechanical zero obtained with the inflatable cuff. A zero line is drawn under both coronary flow curves. For the ascending aortic flow, the position of the trace during diastole is used as a zero reference.

SUMMARY

Using the techniques described, it has been possible to obtain good recordings of aortic and coronary blood flow for periods of up to four months. The experiments are generally terminated by design or because of instrument failure, but not because of vessel erosion or rupture.

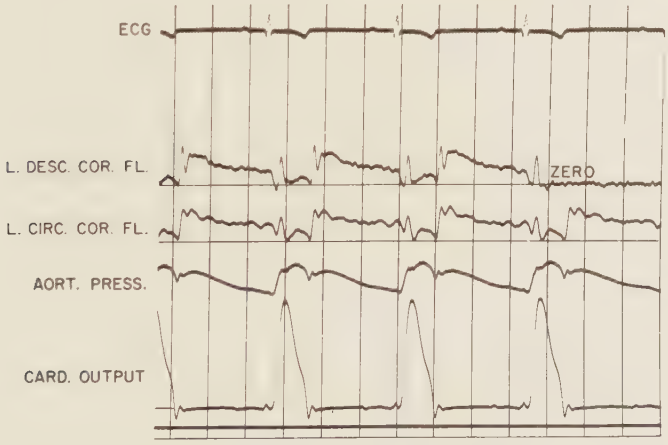

Fig. 3. Typical coronary artery and central aorta flow recordings. The vertical lines are 0.2 sec time intervals.

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29. IMPLANTATION PROCEDURE FOR ARTERIAL FLOW MEASUREMENT ON PERIPHERAL VESSELS

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GENERAL ASPECTS

The introduction of the electromagnetic flowmetering technique opened practically a new area of research: the study of the blood supply to various vascular beds with special reference to non-anesthetized animals in chronic experimental conditions (1-7). This has been made possible by the fact that most of the commercially available electromagnetic flow probes are easily implantable around a given vessel and the procedure is associated with relatively little trauma. However, the initial optimism was very soon followed by a more realistic approach since the experiences obtained in acute experiments did not always find a parallel in conditions of chronic implantation.

The reliability of the electromagnetic flowmeter depends to a large extent on good contact between the flow probe and the wall of the vessel. This fact notwithstanding, for long term implantation, it is advisable to select the size of the implanted flow probe a little larger than the vessel itself. In these circumstances, after the healing process has been completed, an intimate contact will be established, and the fibrous encapsulation stabilizes the position of the flow probe. As a consequence, prolonged electromagnetic flow measurements under chronic experimental conditions are usually more reliable than under acute conditions. The artifacts due to movement of the flow probe are minimized, and the tracing remains stable for the duration of several weeks. As a rule, healing and post-operative recovery are faster and relatively more trouble-free in rabbits than in dogs.

In our experiments, flow probes of the following companies have been used: Micron Instruments, Statham and In-Vivo Metric. In about 15% of the implanted animals, it was necessary to terminate the experiments for technical reasons associated with a breakdown in the performance of the probes. When a probe was successfully implanted, it provided useful results for a

period of 3 months; exceptionally, useful life extended up to 6 months.

The following section summarizes our experiences for specific vessels.

SPECIFIC VESSELS

a. Superior Mesenteric Artery (SMA).

The anatomical position of the superior mesenteric artery is suitable for long term implantation of the electromagnetic flow probe, and thus for long term study of blood flow through the splanchnic region. The main advantage resides in the fact that the main stem of the SMA presents a short portion of vessel without ramification, just after it arises from the aorta. This vessel supplies the jejunum and ileum and partially the duodenum, pancreas, and colon. We did not observe many anatomical variations. Flow probes 4-6 mm in diameter were used in dogs weighing 12-18 kg, while in rabbits weighing 2.5 to 3 kg the flow probes were in the 2 to 2.5 mm diameter range. The implantation itself was performed under aseptic conditions using a retroperitoneal approach through a left flank incision. The left adrenal gland was gently displaced caudad; sometimes it was necessary to ligate the adrenal vein. Cephalad from this vein, a pulsating SMA can be observed. We had good experience with a right angle forceps for this dissection since the location of the SMA is rather deep. These forceps can also be used for the positioning of the flow probe. Distally from the flow probe, an occlusion cuff was implanted (8 to 10 mm and 3 mm wide for dogs and rabbits, respectively). With this size of cuff, it was not necessary to tie off any branches of the SMA. The connectors and the external ends of the tubing leading to the occlusion cuffs were brought out into the interscapular region. For this purpose a simple trocar was used, connected on one end to a large Tygon tubing into which the connectors with the tubings could be inserted, and pulled through the skin tunnel.

After several days of healing, a typical flow profile could be observed which usually remained stable throughout the experimental period (Fig. 1). The flow profile in rabbits was somewhat different, mainly due to the higher heart rate and, thence, a shorter duration of the cardiac cycle. A transient bradycardia, provoked by apneusis, for instance (Fig. 2), changes the SMA flow profile to a form close to that observed in dogs.

If the healing process is successful, the animal can be studied for about 3 months, sometimes up to 6 months. Deleterious effects are a consequence of electrical malfunction of the flow probe, usually an electrical leakage, or intermittent connections in the leads; and leakage or rupture of the zeroing cuff. The lack of the mechanical zero flow line severely jeopardizes the results of the whole experiment, at least with the currently available flow

Fig. 1. Cardiovascular changes during experimentally induced dumping syndrome in a non-anesthetized dog. Upper left panel: control tracing. From top to bottom on each panel: BP = arterial blood pressure; AOQ = flow in ascending aorta; SMAQ = flow in superior mesenteric artery; ILAQ = flow in external iliac artery. Upper right panel: 45 seconds after inducing dumping syndrome. Lower left panel: 10 minutes later. Lower right panel: peak of response.

probes. We have had no experience with the newer flow probes which claim reliable electrical zero. In the absence of a reliable mechanical zero, the zero flow line can be established by extreme bradycardia or even during heart standstill elicited by i. v. injection of 2.4 μg of acetylcholine. However, this approach is sometimes not satisfactory due to collapse of the vessel wall if encapsulation is incomplete.

Deleterious effects may also result from changes in the vessel wall. These alterations usually indicate an imminent end of the experimental period. In this context it was noted that a stenosis of the vessel usually does affect immediately either the characteristics of the flow profile or the flow

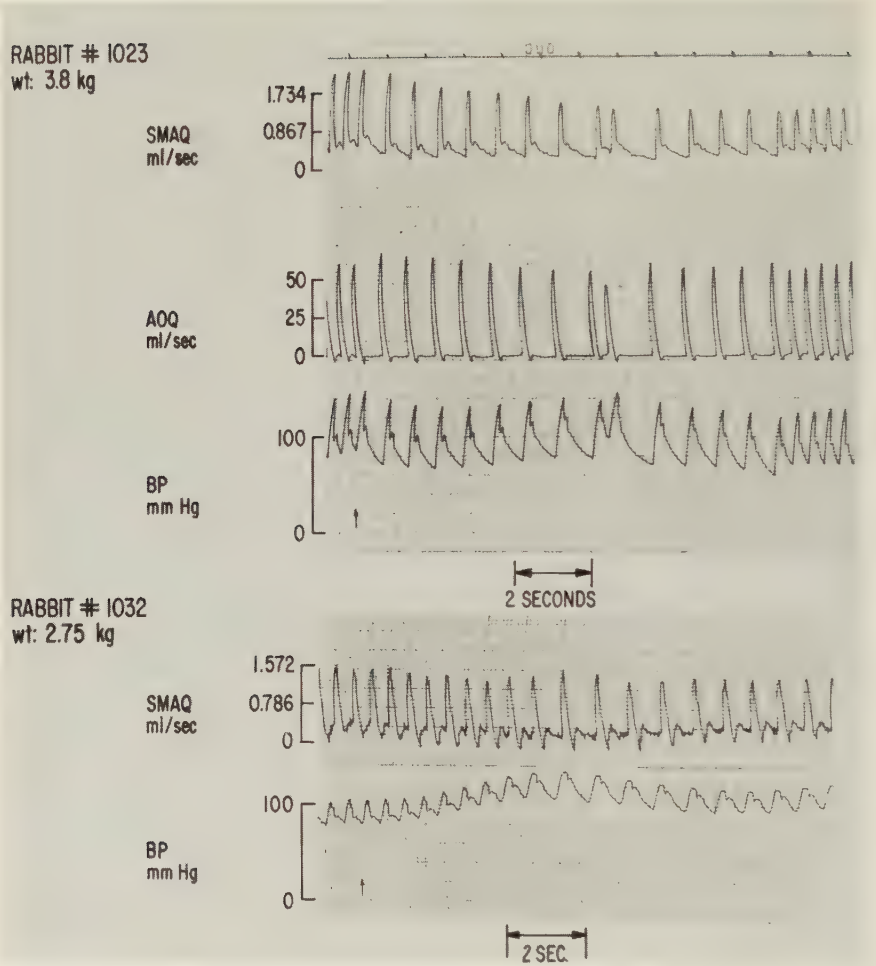

Fig. 2. Changes of cardiovascular function in a non-anesthetized rabbit. Arrow indicates beginning of apneusis with change in blood pressure and heart rate.

rate. It is interesting that the first sign attributable to stenosis is a sudden increase in arterial blood pressure of up to about 50 mm Hg. Two or three days later, the blood pressure returns to the initial normal value, but the blood flow in the SMA drops precipitously. This can be explained by the increased flow resistance with transient compensation by an increased arterial pressure. A slow development of SMA constriction is more frequent in rabbits; the preceding increase in arterial blood pressure is not observed.

b. *Renal Artery (RA).*

The renal artery in dogs is smaller than the SMA. The flow probe diameter is accordingly smaller (3 to 4mm). The basic surgical approach is similar to that previously described for the superior mesenteric artery. The left renal artery is always the fourth palpable vessel branching off the aorta below the diaphragm. Renal artery dissection is easier than the SMA, but the post-operative success is less certain because of the relatively long stretch of vessel without solid support. The size of the zero cuff is the same as for the SMA. Exteriorization of the connectors is also accomplished in the same way.

The flow profile depends very much on the site of implantation. If the flow probe is close to the aorta, the configuration is similar to that of the SMA. If the flow probe is located more distally, the configuration of the flow profile is characterized by a typical systolic upswing after the ascending aortic upswing, followed by a precipitous downswing at the end of systole (Fig. 3). Anatomical changes in the renal artery usually lead to an abrupt decrease in the renal artery flow signal; this is not accompanied by

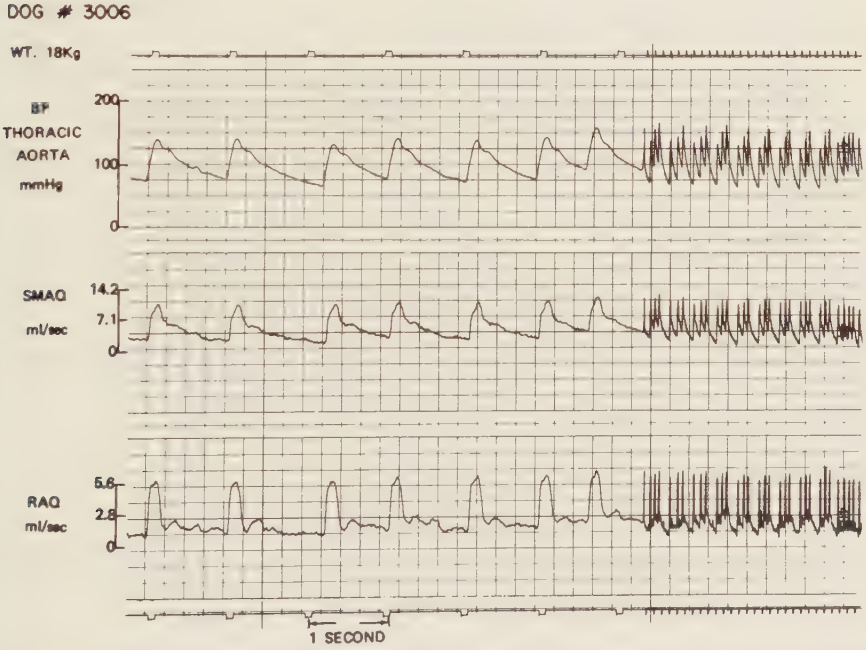

Fig. 3. Steady state flows in non-anesthetized dog. RAQ = renal artery flow. The rest of the abbreviations are as in previous figures.

changes in other hemodynamic functions, perhaps due to the fact that this is a paired organ.

c. *Iliac Artery (ILA).*

We selected the iliac artery blood flow as the representative vessel for skeletal muscle flood flow. We tried repeatedly to implant flow probes around the femoral artery, but without sufficiently long lasting results. Therefore, we decided to implant the flow probe in a more protected area.

The surgical approach to the iliac artery was again from the left side. The incision was parallel to the inguinal ligament about 3-4 cm cephalad. We tried to reach the artery retroperitoneally, but in about 50% of the cases we inadvertently entered the peritoneal cavity. The external iliac artery represents the last branch of the abdominal aorta and the flow probes used in the dogs (12-18 kg) were of 3-4 mm diameter. The artery is relatively long without any branches for several centimeters, and the positioning of the flow probe and the occlusion cuff presents no difficulties. The healing process usually occurs without any complications. Under normal resting conditions the flow profile is characterized by a systolic upswing lagging the ascending aortic upswing by about 70 msec, followed by a precipitous downswing approaching zero at the end of systole, with an oscillation coming back but remaining positive throughout diastole (Fig. 4). When the

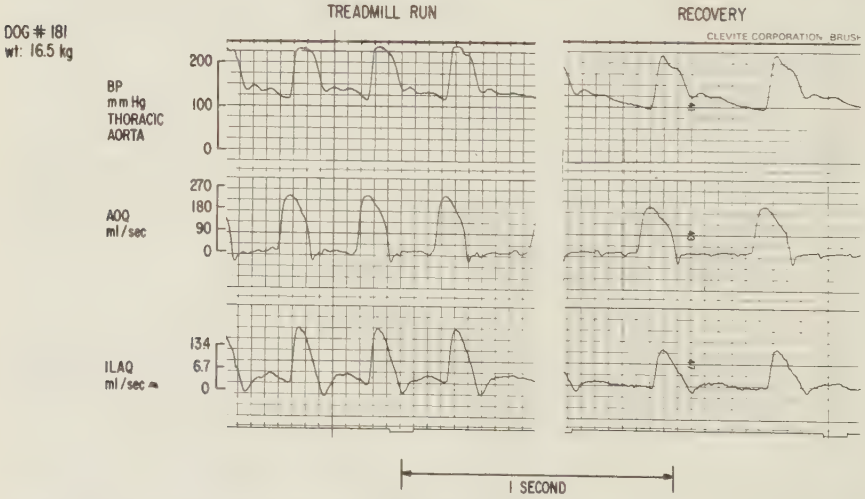

Fig. 4. Cardiovascular changes during treadmill run and following brief recovery. ILAQ = iliac artery blood flow.

iliac artery blood flow increased due to muscular exercise, usually a post-systolic negative dip was observed, characterizing backflow (Fig. 4), (7-9).

d. *Brachiocephalic Artery (BCA).*

The brachiocephalic artery carries the blood supply to both common carotid arteries, the left vertebral artery, and the left foreleg. We selected this artery mainly after our failures to maintain a properly functioning flow probe around the common carotid arteries. The surgical approach in this case is through the third intercostal space as in the case of the ascending aorta. The BCA is the first branch arising from the ascending aorta after the coronary arteries. The dissection presents no difficulties, and a flow probe of 6-7 mm in diameter is usually required in the dog. The leads, as well as the tubing of the occlusion cuff, were brought out through the chest opening, funneled under the skin, and exteriorized at the interscapular region. Because of the good protection of the flow probe in the thoracic cavity, complications with the implantation site were minimal.

The flow profile depends upon the position of the probe, but it remains constant for a given animal (Fig. 5).

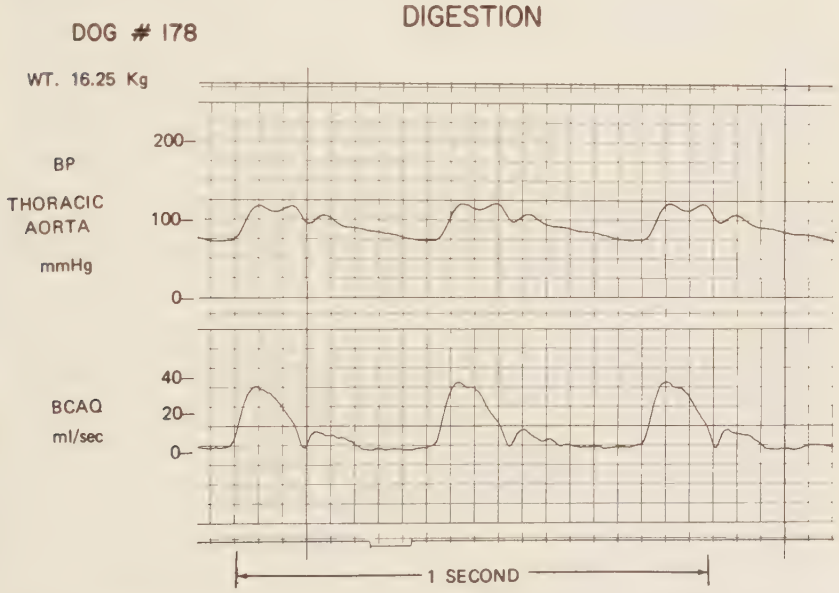

Fig. 5. Simultaneous recording of blood pressure in thoracic aorta and blood flow in brachiocephalic artery (BCAQ).

SUMMARY

Measurement of peripheral artery blood flow under chronic experimental conditions may be considered a routine experimental procedure provided that some precautions are taken: proper size of flow probes, aseptic procedure, suitable site of implantation, and good post-operative care.

In general, the reliability of electromagnetic flow measurement appears to be better under chronic conditions, since the growth of fibrous tissue secures a more constant position of the probe and a more reliable contact with the vessel. For similar reasons, results with flow probes implanted around superficially located arteries or those exposed to motion (femoral and carotid arteries) have been rather disappointing. Best results can be expected with vessels not exposed to changing stretch. The only basic difference associated with implantation of flow probes in dogs and rabbits appears to be the faster healing process in rabbits.

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30. INTRACRANIAL IMPLANTATION OF FLOWMETERS ON THE MIDDLE CEREBRAL ARTERY IN THE PRIMATE

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Recent developments in the microsurgery of blood vessels intracranially, popularized by Yasargil and others (1-3) and made possible by the use of the operating microscope, have opened the field of cerebral blood flow to direct study and chronic instrumentation. Small electromagnetic probes have been used on cerebral arteries in the primate and dog in acute experiments for a number of years (4-6), but accurate chronic measurements of a direct nature have only recently been possible with the development of small implantable flowmeters. A skilled surgeon using an operating microscope can accomplish the implantation in the smaller primate in less than three hours and in the baboon or chimpanzee in less than four. However, meticulous attention to details is a prerequisite for any kind of success and minor errors will inevitably lead to experimental failure.

As in human neurosurgery, a thorough knowledge of primate anatomy is essential (7-10). Publications emphasizing numerous anastomoses in the vascular supply to the brain in the dog (11, 12) make most extrapolations concerning the physiology of the dog's cerebral blood flow to the human more speculative because of the fact that these fundamental anastomoses must be ligated to isolate the cerebral circulation. Thus, the primate is the more logical experimental animal to use. In recent experiments the Macaca mulata demonstrated some similarities to the human in regard to autoregulation and surgery is easier than in the baboon. Moreover the Macaca's intracranial arteries are about the same size as the larger primates. As one can easily see from the skull of the baboon, the sharp slope of the sphenoid ridge makes the surgical approach difficult (Fig. 1). The limiting factor in the baboon, however, is the extremely large masseter muscle group which must be incised in order to approach the floor of the middle fossa and gain access to the origin of the middle cerebral artery. Incision of the muscle group creates severe post-op feeding problems and we have had to resort to tube feeding in these animals. However, the approach used in the baboon is

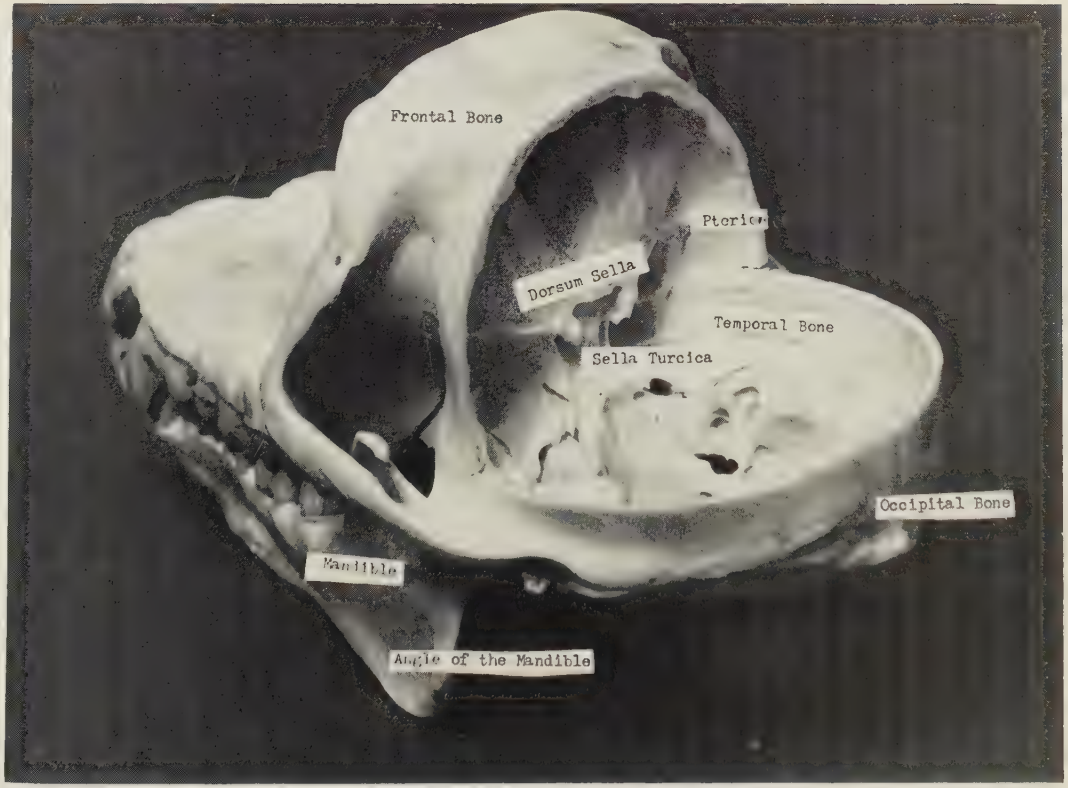

Fig. 1. Baboon skull demonstrating negligible frontal fossa, steep sphenoid ridge and very deep distance between zygoma and front temporal bone which is occupied by huge muscle.

the same as that used in the Macaca mulata and the chimpanzee. Thus in the following description of the operative technique the baboon will be used as the example, but all landmarks and approaches can be equally applied to either of the other two animals mentioned.

The animal is anesthetized with phencyclidine hydrochloride at a dose of .6 mg per kg body weight and .2 to .3 mg of atropine is given intramuscularly to prevent excessive salivation. The hair is shaved off the head and the neck with an electric razor and then further shaved with a straight blade, and an intracath is placed in a peripheral vein for the administration of fluids. An endotracheal tube is placed in the larynx and into the trachea and connected to an anesthesia machine which administers halothane and nitrous oxide. A heating pad under the animal prevents excessive loss of body heat. This is a very important step since body heat loss from these animals, particularly with the hair clipped, may be excessive and must be kept to a minimum. The skin is prepped with soap and then draped in a sterile fashion. In placing the drapes, care must be taken to get them well above the zygoma and along the supraobital ridge.

An incision is made approximately 1 to 1.5 cm from the supraorbital ridge and then down over the zygoma for about 2 cm. This lower limb may later have to be extended. The skin incision is then swung along the midline, usually about 2 cm lateral to it, then dorsocaudad toward the occiput. Wound clips for hemostasis are applied to skin edges through gauze to protect the edges of the skin. The skin flap is then elevated off the temporal fascia and held back over folded sponges with a towel clip and rubber bands or suture and protected with a moist sponge. Using electrocautery, the temporalis fascia is incised and the temporal masseter muscle is elevated off the skull with a periostial elevator. There will be bleeding from vessels coming out of the junction of the tempero-pterygo-palatine bones and this bleeding will stop with coagulation and bone wax. The muscle is retracted with Gelpi self-retaining retractors. In many instances three of the retractors are necessary, particularly in the baboon. It is mandatory that the slope of the interior zygomatic process as well as the tempero-pterygo-palatine suture be identified as this marks the pterion in these animals. If that suture has not been reached or muscles protrude so that one does not get a good direct view over the edge of the zygoma, then enough muscle has not been incised, retracted or removed. Often a sponge shoved down below the zygoma into the muscle mass of the masseter will help.

A burr hole is made manually or with a power drill and the craniectomy, in a deltoid or rhomboid shape, is fashioned with a rongeurs. Further profuse bleeding will occur from the bone overlying the temporal fossa. This must be controlled with wax and will be worrisome. A craniectomy is

carried up to the orbit anteriorly and well down past the pterion into the temporal fossa inferiorly and back into the frontal bone usually to about the coronal suture. The edges of the craniectomy are waxed and then gel-foam strips are placed between the dura and the cranial vault along the craniectomy. Small strips of cottonoid are placed along the edges of the dura which is then incised with a number 15 knife blade along the frontal edge and medially. The free edges are then tacked with 5-0 sutures. The operating microscope is then moved into the field for use in the next part of the operative procedure.

The frontal lobe is retracted and cottonoids placed in such a fashion as to elevate the sylvian fissure off the sphenoid ridge. Usually the middle cerebral artery can be seen beneath the arachnoid in the fissure. With a blunt hook, the arachnoid is opened and the branches of the middle cerebral artery identified. With the flow probes used currently, at least 1.5 to 1.8 cm or more of branch-free artery must be obtained for implantation. Care must be taken to use the bipolar coagulating forceps well away from the artery; moreover, the forceps must be scrupulously clean and used to coagulate intermittently for short intervals lest they stick to the artery or brain. To avoid damage, the artery must never be grasped with forceps and only handled with a blunt right angle hook. Extreme care must be taken to prevent cortical damage in pulling the artery away from the cortex itself. It is usually necessary to advance all the way down the sphenoid ridge to the anterior clinoid process and dissect enough arachnoid away from the artery to make sure the largest portion is selected for probe placement. This usually requires use of one hand for retraction with a metal ribbon on the fissure while dissecting with the other. An assistant is too heavy-handed and the hole too small for more than one pair of hands to be working at one time.

Once the segment of artery has been obtained, a 2 mm diameter Doppler flow probe is moistened in warm sterile saline. A lead wire from the flow probe is grasped with a pair of bayonet forceps while the artery is tilted away from the cortex with a blunt hook. In order for this to be possible, cottonoids will have had to be packed in position. One wire of the two wires is then slipped between the cortex and the artery and pulled under it. Gradually under direct microscopic control the entire length of lead wire is worked under the artery. The tie suture for the probe similarly must be advanced under the artery. The probe is then slipped into the wound and gently slipped under the artery using bayonet forceps with one hand while the other is pulling the artery into position with the blunt hook. Care must be taken not to tear the artery with the hook nor to get the hook tangled up in the probe wires or probe housing. Once the probe is in position, the suture closing the probe is tied first with a surgeon's knot and then with an overhand knot using two bayonet forceps (Fig. 2). The

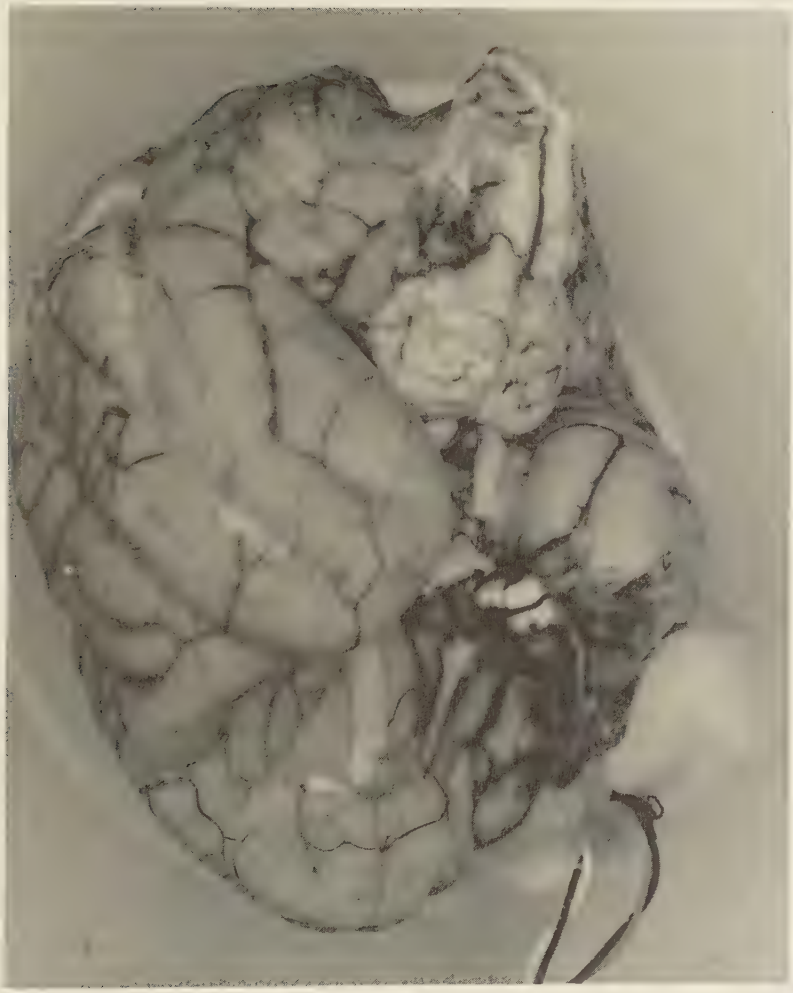

Fig. 2. Doppler flow probe in place in specimen injected with red latex. Cranioplasty material is still attached to lead wires. Moderate contusion and subarachnoid hemorrhage at operative site are visible.

lead wires from the probe are tied with sutures used to close the dura. The dura is closed with 5-0 silk. A cranioplasty is then made. If the material used is exothermic, care must be taken to keep it from becoming too hot. Copious cold saline irrigation must be used. The muscle is then pulled back into place and the temporalis fascia reapproximated with 3-0 suture.

Once the muscle has been pulled together a tunnel is made between the fascia and the skin down to the back of the animal's neck. The lead wire coming from the cranioplasty is then passed down this tunnel and left encapsulated on the back of the animal's neck. A subcuticular stitch of 3-0 suture is used to reapproximate the edges of the skin flap. The skin itself is closed with 4-0 wire. The wound is washed with soap and the animal is allowed to wake up from the anesthesia. At the appropriate time the endotracheal tube is removed.

During the recovery period, immediately post-op, the animal is given steroid and antibiotic therapy. The steroid therapy is used to cut down on brain swelling. This lasts for approximately two days. Antibiotic therapy has routinely been given for approximately 5 to 7 days.

This procedure just described has been used in a total of seven chimpanzees, seven baboons and over 30 Macaca mulata monkeys. In all of these animals, immediately following surgery, a period of monoparesis is always evident. However, after 3 to 5 days this disappears and the animal returns to normal neurological function with no apparent deficit. It is very surprising that many of these animals have tolerated ligation of several large branches off the middle cerebral artery, but no lasting neurological deficit has been seen in any of the animals used in the studies with this technique.

In conclusion, it must be reemphasized that meticulous care is required in all areas of this particular surgery, much more so than in any other place in the body, since the least mistake here will mean the demise of the animal preparation. Successful implantation of probes in the middle cerebral artery has been accomplished for a period of two to four weeks. During this period of time, for some reason which is not known at present, the middle cerebral artery gradually becomes occluded by clot formation. Over this four week period in all animals studied to date, the development of collateral circulation has prevented any specific neurological deficit in the animals in which the middle cerebral artery has been completely occluded.

SUMMARY

Present advances in neurosurgery have permitted the implantation of small flow probes around vessels inside the cranium. The blood flow to the brain has not been studied from an intracranial standpoint until very recent-

ly, and has not been studied at all by the intracranial use of chronically implanted flow probes. Doppler flow probes have been successfully implanted around the middle cerebral artery in monkeys, baboons, and chimpanzees. The technique requires a great deal of microsurgical skill. Success depends upon proper isolation of the artery without undue trauma. Postsurgical complication of motor loss has usually lasted no longer than 6-7 days. From this point forward no clinical signs of any neurological defect can be found. This method has allowed the first direct end-artery determination of cerebral flow properties. Of the three types of animals studied with this method, the best has proven to be the monkey because of availability, maintenance, and cost.

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31. METHODS FOR CHRONICALLY IMPLANTING CORONARY ARTERY BLOOD FLOW PROBES, ARTERIAL OCCLUDERS AND CORONARY SINUS CATHETERS[1]

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CORONARY ARTERY FLOW MONITORING

The great advances in electronics made within the past 15 years (1) now permit the chronic implantation of blood flow sensors on the arteries perfusing the heart. The two coronary arteries most frequently studied in the dog are the circumflex and the anterior descending branch of the left coronary artery. The circumflex branch, being the larger of the two, carries more blood, and thus has a better signal-to-noise-ratio than does the anterior descending branch. The primary disadvantages of using the circumflex are: 1) the vessel is oriented along the short axis of the heart, making stabilization of the probe on the beating heart somewhat difficult, and 2) surgical accessibility is very poor when entering the thorax through the sternum. The anterior descending branch of the left coronary artery, although smaller in diameter than the circumflex, is oriented in the long axis of the heart, thus affording a more favorable arrangement for stabilization of the probe. Also, since the studies in our laboratory required thoracic entrance through the sternum (for coronary sinus catheterization), we chose to place our flow probes around the anterior descending branch.

The style of precalibrated probes (2) used in these studies was a modification of a standard electromagnetic flow probe (400 series, Carolina Medical Electronics, Inc.), in which the cable comes off the probe at right angles to the artery. This modification allows the probe cable to be directed away from the vessel rather than along it, thus making it possible to suture the cable to the epicardium without interfering with the artery through which flow is being measured (Fig. 1). This probe is also supplied with

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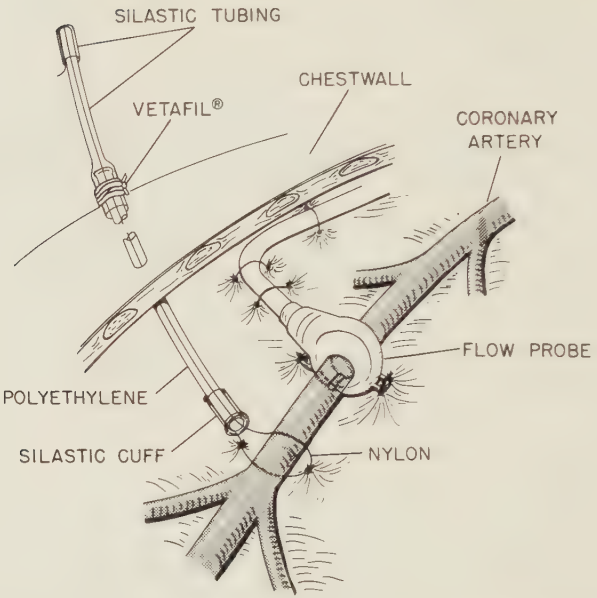

Fig. 1. This arrangement of blood flow probe and snare occluding device was found to be satisfactory for chronically evaluating coronary hemodynamics.

eyelets that permit the probe to be firmly sewn to the epicardium. In our experience we have found that the eyelet under the probe cable needs only one suture, while the opposite eyelet needs two sutures directed out from the probe at right angles from each other. This "triangulation" prevents the probe from rocking back and forth on the long axis of the vessel. This probe is also somewhat smaller than the standard 400 series, has a lighter-weight cable, and comes equipped with a "slot-block" which allows the opening of the probe to be closed when placed around the vessel, thus preventing its accidental disengagement from the artery.

ARTERIAL OCCLUDING DEVICES

Any time electromagnetic probes are used to measure blood flow, provision must be made for periodically checking zero flow. Up to now the attempts to do this electronically have met with minimal success. At the present time there is only one sure way to check zero flow, and that is to provide a device that can transiently stop flow by complete occlusion of the vessel through which flow is being monitored. The only vessel in the body in which reliable zero flow determination may be obtained without complete occlusion is the ascending aorta, because, if the aortic valves are competent, the diastolic flow value is very nearly zero (3). Therefore, an occluding device should be provided for all other vessels and must be placed downstream to the probe a distance of at least two vessel diameters. If the occlusion site is upstream to the probe rather than downstream, or if the occlusion is made too close to the probe, the vessel wall will be drawn away from the electrodes, giving an erroneous zero value.

We will not attempt to discuss all of the various styles of occluders that have been used. However, some of the characteristics of two of the most commonly used varieties—hydraulic occluders and snare occluders—should be mentioned.

The hydraulic occluder is so designed that a small balloon inside a cuff placed around the vessel can be inflated through an exteriorized catheter, causing vascular collapse (1, 4, 5). There are four basic problems with this type of occluder: 1) often the balloon will slip out of the cuff, preventing complete occlusion of the vessel; 2) a relatively long segment of artery is required, often as much as 5 mm; 3) the inside of the catheters and balloons are very difficult to sterilize; and 4) these occluders do occasionally burst during inflation.

The snare occluder (6) consists of a thread of nylon or some other material placed around the artery with the ends leading through a tube or catheter to the exterior of the animal. The primary disadvantages of this type are: 1) the likelihood of damaging the vessel when the threads are drawn tight; 2) the lead-out tube for the threads must be open to enable the snare to slide freely, a procedure that allows air or other materials to enter the body; and 3) the snare may easily become twisted around the artery, preventing the proper release of the occlusion. The snare, however, does have the advantage of requiring only a very small segment of artery for occlusion. This characteristic was so important to our studies that we set about to design a more reliable and less dangerous snare-type occluder for implantation on the coronary artery.

The final workable variation (Fig. 1) consists of a 12-inch-long Intra-

medic polyethylene tube (PE 160, .045 inch I.D., .062 inch O.D.) which was flanged on both ends. A 3-inch segment of Silastic Medical Grade tubing (.045 inch I.D., .085 inch O.D.) was pulled over one flanged end of the polyethylene tube and tied with Vetafil. A Silastic cuff (.062 inch I.D., .125 inch O.D.) was forced over the other flanged end of the polyethylene tube. An 18-inch length of supersoft nylon (4 pound test) was then inserted between the polyethylene tube and the Silastic cuff and knotted so that it could not be drawn back under the cuff. This nylon line was then placed under the artery approximately two vessel diameters distal to the flow probe and threaded through the polyethylene and Silastic tubing in the manner illustrated (Fig. 1). The other end of the Silastic tubing was then closed with a short Silastic cap, the same size as the Silastic cuff. One end of this cap was filled previously with clear adhesive and allowed to dry. The nylon snare extended out between the Silastic tubing and Silastic cap. In this manner the Silastic cap served to stabilize the end of the nylon snare as well as block the end of the tubing, thus preventing a pneumothorax or entrance of materials into the thorax. The nylon line was then sutured to the epicardium for a distance of about 1 mm on each side of the artery. When an occlusion was desired, gentle stretching of the exteriorized Silastic tubing resulted in tightening of the snare. The arrangement of the snare-stabilizing sutures on each side of the artery was such that when the epicardium was pulled up around the vessel, an occlusion was effected. With the epicardium pressing on the artery, the nylon snare does not cut through or damage the vessel. When the Silastic tubing is released, the elasticity of the epicardium, together with the return of the distorted Silastic tubing to its resting length, permits the snare to relax, allowing resumption of blood flow. The pericardium was then closed and a puncture wound made between the ribs. The free end of the occluder was withdrawn as far as possible without placing undue tension on the artery. This free end was then imbedded under the skin until a zero check was needed.

CORONARY SINUS CATHETERIZATION

To place a permanent catheter into the coronary sinus and at the same time maintain vessel patency for obtaining venous myocardial blood samples has proven quite difficult. We have experimented with a number of commercially available catheters, but have found none sufficiently flexible to ride within the beating heart without rupturing the coronary sinus. Also, these catheters are difficult to situate permanently in the desired position. However, we were able to design and implant a satisfactory catheter.

After investigating a number of synthetic materials, Silastic Medical-

Grade Tubing (.045 inch I.D., .085 inch O.D.) was chosen because of its tissue inertness and flexibility. A segment of this tubing was cut to a length of about 16 inches and a series of six small lateral holes punched into the sides of one end of the tubing (Fig. 2). A ball of Silastic adhesive was placed on the exterior of the catheter approximately three cm from the tip. A stylette, fashioned from Medical-Grade Vinyl tubing (.036 inch O.D.) was permanently affixed with silicone adhesive to one end of a Silastic tube (.062 inch I.D., .125 inch O.D.), approximately one centimeter long. The adhesive completely closed off one end of the Silastic tube. This capped stylette was then inserted into the heparin-filled (5000 unit/cc) Silastic catheter so that the cap fitted over the distal end of the catheter. The stylette was cut to the same length as the catheter.

The right atrial appendage was grasped with a pediatric atrial clamp and a purse string suture placed around the tip. The appendage was then cut between the sutures and the catheter inserted toward the posteriolateral aspect of the heart until the catheter could be felt in the atrioventricular groove beyond the post cava. The position of the Silastic ball was located by palpation and the catheter advanced until this ball was directly under the post cava. In advancing the catheter, care was taken to avoid blocking the coronary sinus with the Silastic ball. Sutures were then placed through the atrial wall and around the catheter on each side of the ball (Fig. 2). These sutures stabilized the catheter so well in the coronary sinus that at autopsy the catheter tip was found to extend into the great coronary vein. The

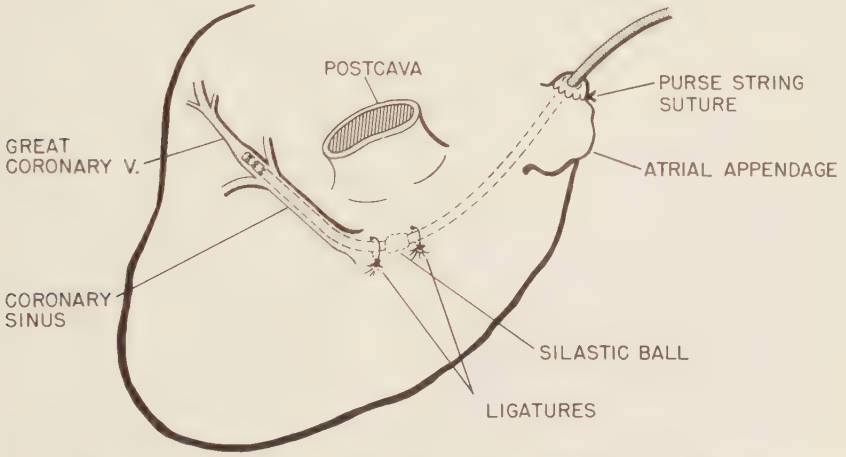

Fig. 2. Illustration of surgical placement of a Silastic catheter into the coronary sinus. See text for description of construction.

catheter was brought out of the thorax through a stab wound between the ribs and positioned between the ribs and the skin. At the time of the experiment a skin incision was made, the catheter was exteriorized, and the stylette withdrawn in order to allow blood sampling.

METHOD FOR DETERMINING THE TISSUE PERFUSED

When studying blood flow through the heart or any other tissue it is convenient to normalize the flow values obtained in terms of ml/100 grams of tissue perfused. This normalization procedure permits ready comparison of the data obtained with previously published values. For determining the amount of myocardial tissue perfused by the segment of artery through which flow was monitored, we used the procedure illustrated in Figure 3.

At the end of the acute phase of the experiment the thorax was opened and the heart removed. The excess adipose tissue, large vessels and pericardium were removed and the total heart weighed. The right coronary artery was cannulated through its coronary ostium and the cannula, connected to a 10 ml syringe, filled with normal saline. The common left coronary artery was exposed and ligated. The anterior descending branch of the left coronary artery was then doubly cannulated in both proximal and distal directions at the precise site previously occupied by the flow sensor. Care must be taken to insure that these cannulae are not inserted into the arterial lumen for a distance greater than absolutely necessary; otherwise, small side branches will be occluded by the cannulae. These two cannulae were then connected to two additional 10 ml syringes in a manner similar to the right coronary artery cannula. The syringe leading to the proximally directed cannula was also filled with normal saline; the distally oriented syringe was filled with India ink. Through a series of Y-tubes the three syringes were connected to a mercury manometer and a pressure of approximately 100 mm Hg was simultaneously applied to the fluid in all three syringes. This system results in an equal and constant perfusion pressure being applied to all areas of the myocardium. The dye injected into the distal segment of the anterior descending coronary artery will stain only the tissue that is normally perfused by that segment of vessel. This tissue can be dissected easily from the unstained tissue and weighed. If a lower pressure were applied to the other vessels, some of the dye would perfuse tissue via collateral channels not normally perfused, and the flow normalization based on a hundred grams of tissue would be erroneously low (7). In our studies we found that the coronary flow was 70 ml/100 grams (SEM ± 6 ml/100 gms) of tissue which was in excellent agreement with Green (8). If one wished to approximate the total myocardial flow, the total heart weight can be divided by 100 and multiplied by the flow per 100 grams of tissue.

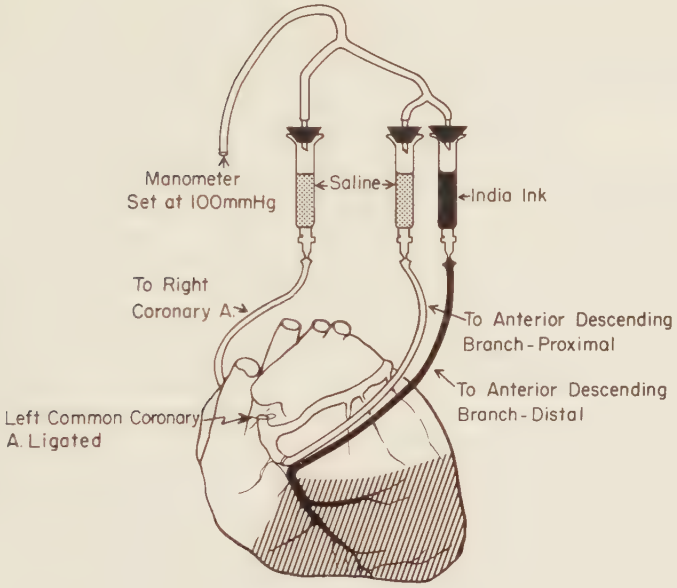

Fig. 3. Constant pressure coronary perfusion system.

SUMMARY

This paper presents techniques for chronic monitoring of coronary vascular and myocardial function and includes a critique of various surgical approaches for the implantation of coronary artery blood flow probes and arterial occluding devices. The fabrication and use of a Silastic catheter suitable for chronic monitoring of coronary sinus blood constituents is presented, as well as techniques for determining the mass of myocardial tissue perfused by that segment of the coronary artery through which flow had been measured.

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32. IMPLANTATION TECHNIQUES FOR VENOUS FLOW MEASUREMENT[1]

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The availability of electromagnetic and ultrasonic flowmeters to record pulsatile blood flow has resulted in many attempts in recent years to record flow in chronically implanted animals under essentially normal conditions (1-3). Flowmeter probes are implanted about the vessel in which flow is to be studied, using sterile operating techniques, and the animal is allowed to recover from surgery. He may then be connected directly to a flowmeter or to a radio transmitter, when the animal to be studied is moving freely about the laboratory or under free ranging situations (3). A number of technical difficulties are inherent in such studies. The major ones are: 1) difficulty in obtaining good electrical contact between the flow probe electrodes and the vessel wall in the case of the electromagnetic flowmeter, or good acoustical coupling in the case of the ultrasonic flowmeter; 2) physico-chemical problems with the flow probes themselves—excessive absorption of moisture, breakage of wires, carbonizing of wires by pulsed currents, etc.; 3) alteration in the normal flow through the vessel due to excessive constriction, scar tissue formation, kinking by the probe, and denervation; 4) difficulties with infection, particularly the development of chronic sinus tracts along the wires; and 5) problems related to calibration and zero flow determination for the flow probe.

This paper is aimed at discussing the more common of these problems, particularly relative to the electromagnetic flowmeter. It will deal primarily with the problems of venous flow measurement, which are somewhat different in nature from those for arterial flow, although often the discussion may be equally applied to both situations. Perhaps the major differences lie in the lack of rupture, in the venous flow case, of the vessel, as frequently occurs in arterial flow measurement; the lack of good pressure contact between the vessel wall and the probe electrodes; and, perhaps, the ability

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to constrict the veins somewhat more than the artery without significantly altering the flow patterns because of lower peak velocities of flow.

TRANSDUCER FIXATION

In our early experiments we found that despite the fact that some of the venous flow probes were implanted for a period up to two months with extensive scar tissue formation around the outside of the probe, scar tissue would not form between the vein itself and the smooth inner surface of the flow probe. This meant that a slight shifting of the flow probe or any attempt to obtain zero flow might result in loss of contact between the vessel wall and the flow probe. In an attempt to alleviate this problem two methods have been devised, one of which is considerably easier than the other from a strictly surgical standpoint. In one method, strips of Dacron grafting material approximately ¼ inch wide are sutured to the adventitia of the vein above and below the probe. The strips pass on the outside of the probe on 3-4 sides and pull the vein wall tightly against the probe. 5-0 Dacron mattress sutures are used; the strips are also sutured to the umbilical tape holding the probe halves together to prevent lateral motion. This method is quite satisfactory, but does require considerable time and surgical skill. Figure 1 illustrates the flow probes in place around the inferior and superior vena cavae and the ascending aorta. Note the Dacron grafting strips and the tied azygos vein.

The second method consists of the use of a biological glue to hold the wall of the vein against the inner surface of the probes. The glues used have been n-butyl-2-cyanoacrylate monomer and its isobutyl analog (obtained courtesy of Ethicon, Inc.). A drop of glue is placed on the vein and the vein wall pushed against the flow probe. The procedure is carried out in three or four locations around the circumference of the vein wall at each end of the flow probe. Following application of the glue, the electrode to animal resistance is measured with an ohmmeter to verify that no glue has actually come into contact with the probe electrodes. The glue can form a high resistance coating over the electrodes and prevent the flowmeter from operating properly. The glue dries very rapidly requiring only that the vein wall be pushed against the inner surface of the flow probe for a few seconds. After initial contact is established, additional glue may be applied to strengthen the bond if necessary. These methods enable one to hold the vein tightly against the inner surface of the probe and immediate recordings of venous flow may be obtained.

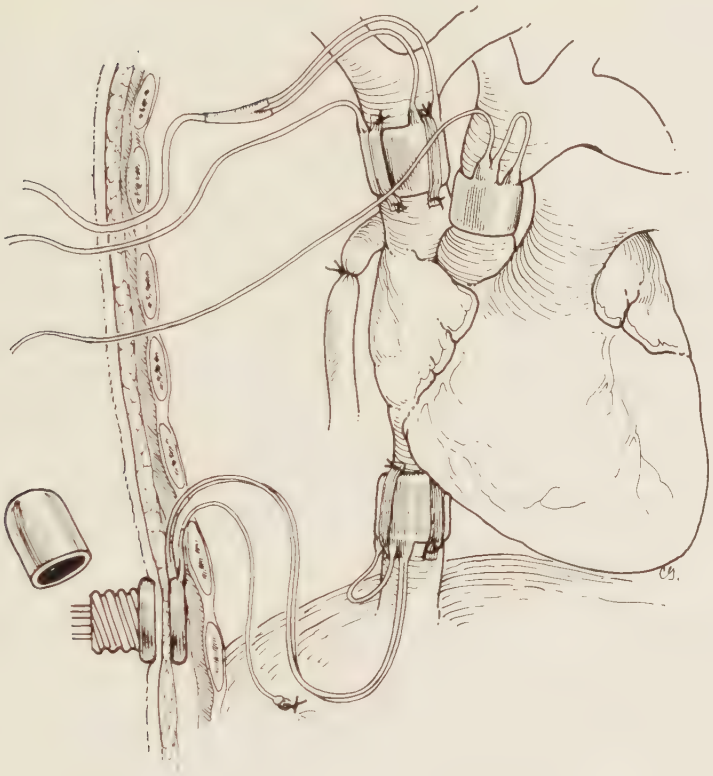

Fig. 1. Flow probes in place for measurement of ascending aortic, superior and inferior vena caval blood flow. Reproduced, by permission, from *American Journal of Physiology* 215:1059, 1968.

LEADS AND EXTERIORIZATION

The probe leads should be coated with Silastic rubber, and are also pretreated with Monocote (Reheis Chemical Co.) prior to use to reduce the foreign body reaction.

The leads are brought through the intercostal space nearest the probe, keeping the intrathoracic portion to a minimum thus further decreasing the extent of any reaction. The leads then traverse the muscle and fascia in an oblique manner, so that an air-tight tunnel is obtained, and are brought out through a stab-wound in the skin. A 4-0 Tevdek suture (Deknatel, Inc.) is placed around the probe leads both at the chest wall and at the skin surface to assist in obtaining an air-tight tunnel, as well as to prevent inadvertent pulling on the flow probe. Skin lead terminals have also been used through a buttonhole in the skin and held in place with an external ring. These are the usual type of skin lead terminals available commercially (e.g., Statham Instruments). We've had difficulty with infection and skin necrosis around the terminals, particularly if the buttons were tightened somewhat too much, and in general find that simply using the wires themselves without a permanent terminal is more successful.

CHEST CLOSURE AND POST-OPERATIVE CARE

Probably one of the most important aspects of the implantation of probes into the thoracic cavity is to obtain an air-tight closure along with aspiration of the remaining air in the chest. In a dog, it is essentially impossible to suture the pleura closed and it is not feasible to maintain the animal on a suction pump, although some type of small one-way valve might be devised and implanted. We leave in a rubber drainage tube at one side of the incision site and carefully close the incision by layers. When the wound is closed, a syringe and 3-way stopcock are attached to the drainage tube and the chest aspirated. The lungs are then inflated at the same time that the rubber tube is withdrawn and a purse string suture around the tube is tightened. By this means it is possible to get rid of nearly all the air in the chest and have the lungs reinflated. Alternatively the tube may be clamped and left in place for several days, in which case it should be positioned through a stab wound at other than the primary incision site. The animal is checked periodically for a few days with a stethoscope to determine if atelectasis or pleural effusion is present. If radiological equipment is available, films may be taken and observed for effusion, atelectasis, pneumonia, collapse, etc. When large amounts of effusion have occurred, due to an excessive number of implanted devices or poor coating techniques, in some

cases we have been able to aspirate the chest repeatedly and eventually have the animal recover. If air leaks occur along the pathways of the probe leads or the primary incision, this is a much more difficult situation to deal with and is best prevented by careful surgical technique at the time of the implantation. Once developed, it is nearly impossible to cure. Biological adhesive materials (e.g., Skin-hesive, United Surgical) may assist in stopping air passageways, since one cannot suture into these grossly infected areas.

After the probe leads are brought through the skin, the chest incision is covered first with a few 4 x 4 gauze sponges. The probe leads are then coiled, wrapped in a sponge, and held with a rubber band. A large roll gauze bandage (e.g., Kerlix, Kendall) is then placed around the chest of the animal. This is followed by an elastic bandage with suitable tape reinforcement at the edges to prevent the probe leads working out from beneath the bandage. A canvas dog jacket completes the final layer. While this may seem like an excessive amount of bandaging, it does result in adequate protection of the probe leads from the animal scratching against the side of the cage or simply reaching around and getting at it with his teeth. The bandage must not be so tight as to seriously interfere with thoracic cage motion. The dressings are changed frequently for the first few days until they remain dry.

We feel that a sterile operative procedure significantly reduces the scar tissue formation from infection, although the dog and the sheep are two animals which, in our experience, are quite resistant to infection. Post-operatively they are routinely given procaine penicillin, 600,000 units, and streptomycin, 0.5 gram, per day. The use of Bacitracin ointment around the wound site appears to be helpful in preventing localized infections and forming a clean chronic sinus tract where the leads exit from the skin.

The wounds heal rapidly and the skin sutures may be removed in 7-10 days with usually little difficulty with infection. An occasional stitch infection usually ends as soon as the offending stitch is removed.

CALIBRATION AND ZERO FLOW DETERMINATION

The elecromagnetic flowmeter used in these studies was designed by the author and has been described previously (4, 5). The flow probes used should be as light in weight as possible, preferably an air-core type (Zepeda or equivalent). They are calibrated before implantation using dialysis tubing (6) and blood adjusted to the approximate hematocrit of the experimental animal. Hematocrit has about a 5% effect on the calibration for a factor of ten change in hematocrit (7), although this may apparently be reduced by

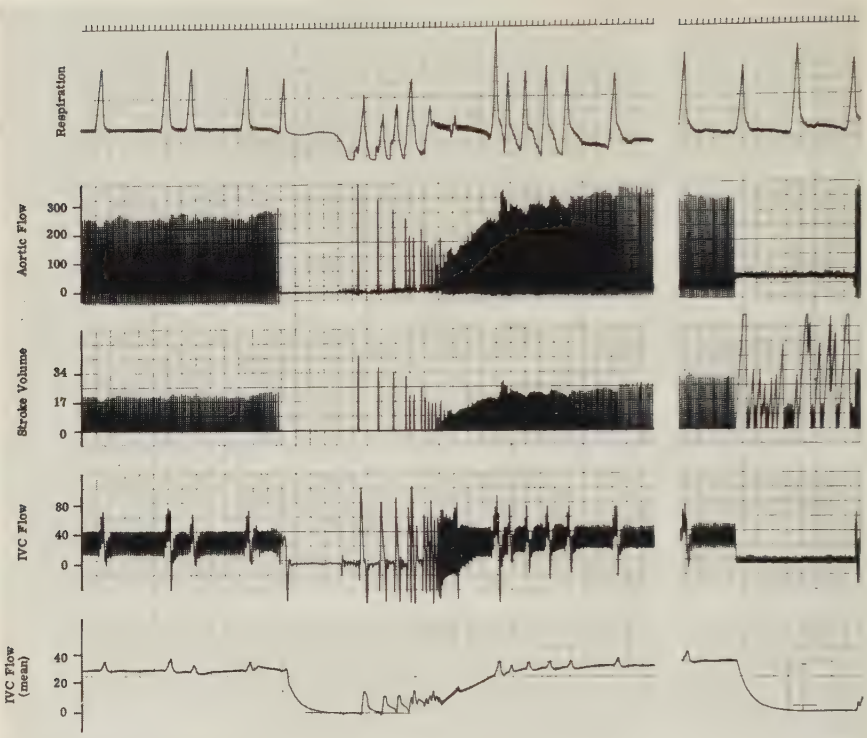

Fig. 2. Injection of 10 mg. acetylcholine to produce transient cardiac arrest in a dog. Magnet off zero in right panel; stroke volume integrator circuit not resetting properly due to zero offset. Flow in ml/sec, stroke volume in ml, time marks in seconds. Respiration from a pneumograph tube around the chest, inspiration is an upward deflection. Reproduced, by permission, from *American Journal of Physiology* 251:1062, 1968.

proper probe design (8, 9). Dialysis tubing obviates the need for storage of vessels and possible changes in the ionic content of the vessel walls. Calibration should be rechecked after removal of the flow probe from the chronic animal. Recently out of date human blood from the blood bank works well in the calibration procedure.

Determination of the zero flow level is very important for venous flow recording because of the frequent presence of backward flow, particularly near the heart (1, 2, 10, 11). Zero flow may be obtained by implanting a Jacobson cuff (Davol Rubber Co.), an inclusion snare device (12, 13), or, alternatively, by injecting acetylcholine. The amount of overall reaction and pleural effusion appears to be directly proportional to the amount of hardware implanted into an animal. We prefer, whenever possible, not to implant occlusion cuffs but to use acetylcholine for zero flow determinations. Large amounts, up to 10 mg, may be injected even into a conscious animal. There will be a brief stoppage of the heart, followed by some gastrointestinal and salivary responses, but with very fast recovery and little or no evidence of associated pain or other side effects. It is merely necessary that a fairly large bolus be given rapidly intravenously. The heart should stop for a period of ten seconds or so. A perfectly flat flow tracing should result, corresponding to zero flow as shown in Figure 2. The only real difficulty is that the animal may respire during the zero flow period and respiration may cause a significant amount of venous flow to occur into the thoracic cavity. If this occurs, the procedure must be repeated. With the probes in situ and adequately tethered it is possible to obtain a known relationship between the "magnet off" zero and the acetylcholine zero with some degree of assurance of stability of the value, thus allowing "magnet off" zero to be used for frequent determinations of zero and only occasionally injecting acetylcholine to check true zero. This method is also not as hazardous as using a snare, which may result in occluding the venous flow for a significant period of time. Occluding the superior or inferior caval flow in an animal for several minutes may result in permanent damage to the animal (14), particularly in the case of the inferior vena cava.

SUMMARY

Techniques for implanting electromagnetic flow probes around large veins, particulary within the thoracic cavity, for chronic animal studies are discussed. The importance of adequate tethering in obtaining a stable zero flow baseline is stressed.

Acknowledgment

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33. A TECHNIQUE FOR MEASURING LEFT VENTRICULAR DIMENSIONS IN CONSCIOUS DOGS USING BIPLANE CINEFLUOROGRAPHY[1]

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The numerous methods for measuring dimensions of the left ventricle have been recently reviewed by Sandler (1). Radiographic techniques utilizing the injection of radiopaque contrast materials for ventricular visualization have been the most widely employed. In addition to the difficulty of using angiographic dye in conscious animals, this technique has the added disadvantage of requiring injection of a material that is known to alter cardiac function (2). Thus, the method to be described was developed to avoid the necessity of catheter introduction and contrast injection. It has proven applicable initially in acute studies (3-5), and more recently in chronic studies in conscious chronically instrumented dogs (6-9). The method as currently applied in conscious dogs will be reviewed in this presentation. A previous publication (5) contains details on equipment specifications and photographic techniques.

Mongrel dogs are prepared for subsequent dimensional analysis by the appropriate placement of six lead beads and two clips through a left lateral thoracotomy. The beads are positioned in order to define the three axes of an assumed ellipsoid shell of muscle near the left ventricular endocardium. Figure 1 schematically depicts the location of the beads and clips and the dimensions they define. The apex bead is sutured to the apical dimple. The other beads are positioned near the endocardium by needle insertion. The needles used to insert the beads are shown in Figure 2. The base bead is inserted just below the origin of the left circumflex coronary artery. The anterior bead is placed to the left but immediately adjacent to the left anterior descending coronary artery halfway between the apical and base

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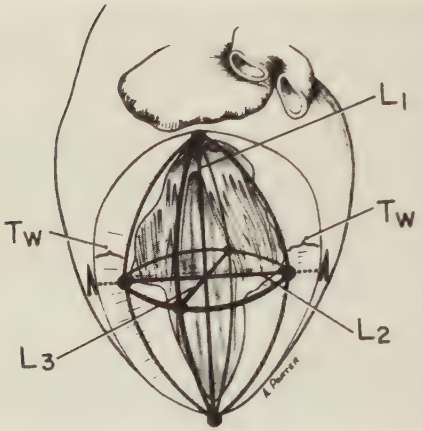

Fig. 1. Schematic representation of the left ventricular dimensions measured. L_1, base-to-apex length; L_2, anterior-to-posterior length; L_3, septal-to-lateral length; and T_W, wall thickness. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

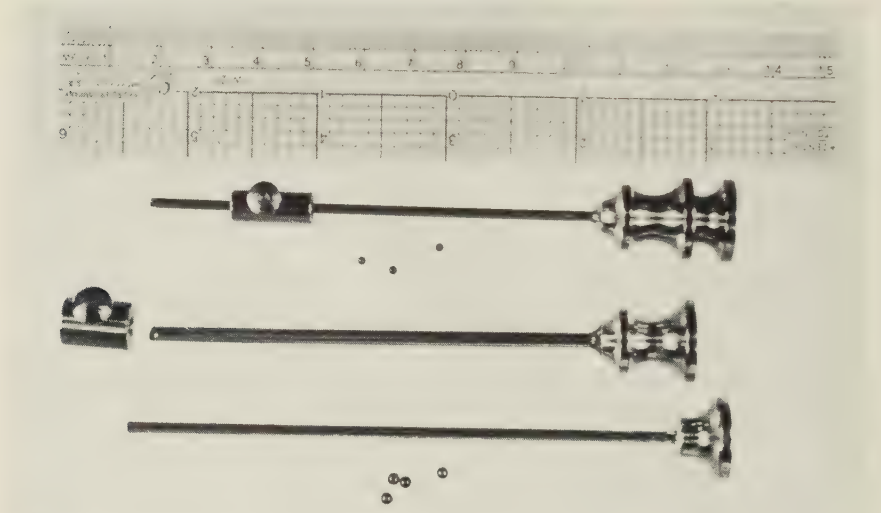

Fig. 2. Needles used to insert beads near the endocardium. The two needle sizes are to accommodate the two bead sizes. Each needle has a stylet and an adjustable stop. The latter is used to set the depth the bead is to be placed, generally 6-8 mm. Also shown are several beads of the two sizes used.

beads. Using the anterior bead as a reference, the three remaining beads are then located an equal distance from the apical bead: the posterior bead is placed adjacent to the posterior descending coronary artery and the lateral and septal beads halfway between the anterior and posterior beads. For endocardial positioning of the base, anterior, posterior, and lateral beads, the needle is inserted 6-8 mm into the left ventricular wall using a variable stop to prevent deeper needle penetration. To position the septal bead, the needle is inserted adjacent to the anterior descending coronary artery and advanced one to two cm into the septum in order to place the point of the needle and therefore the bead in the desired position. The apex, base, anterior, and posterior beads are 2 mm in diameter and the septal and lateral beads are 1 mm in diameter. A silver-tantalum clip is sutured on the epicardium opposite the anterior and posterior beads to complete placement of the dimension markers. Position of the markers is then checked by fluoroscopy.

At this point other transducers for chronic measurement of hemodynamic parameters can be inserted. Currently left ventricular pressure is measured with a solid state transducer (Type P18, Konigsberg Instruments) inserted through a stab wound near the apex; left atrial pressure is measured through a small polyethylene catheter inserted through the atrial appendage, for later attachment to an external transducer; and an electromagnetic flow probe (Statham Instruments) is placed for measurement of ascending aortic flow. After all gauges are positioned properly, the pericardium is closed, transducer cables are exteriorized through the posterior aspect of the neck, the thoracotomy is repaired, and the dog is allowed to recover for a 2 to 3-week period.

The animal is returned to the laboratory and positioned prone in a sling in front of a biplane cinefluorograph (AP and lateral) (Fig. 3). The motion of the implanted dimension markers is recorded on 35 mm film at 16.7 msec intervals (1/60 sec) during simultaneous recording of standard hemodynamic parameters available from the chronically implanted transducers. A pair of biplane exposures is shown in Figure 4.

The biplane film is then processed to determine the absolute distance between appropriate pairs of beads. The specifications of the equipment and techniques used for photographing and measuring the motion of the beads and clips have been presented in detail previously (5). Absolute distances for calibration are obtained from exposures of a spherical lead ball of known diameter (23 or 35 mm), recorded after exposures of the heart, in the same position as the heart. The absolute distances between the base and apex beads (L_1), the anterior and posterior beads (L_2), the septal and lateral beads (L_3), the anterior clip and bead (T_W), and the posterior clip

Fig. 3. A conscious chronically instrumented dog positioned for cinefluorography.

and bead (T_W) (Fig. 1) are then calculated from the measured distances on both simultaneously exposed biplane frames, using the formula:

$$\text{distance} = \sqrt{x^2 + y^2 + z^2} \tag{1}$$

where x = the calibrated vertical displacement between beads on the anterior film, y = the calibrated horizontal displacement on the anterior film, and z = the calibrated vertical displacement on the lateral film. These calculated distances define 3 ventricular dimensions (L_1, L_2, L_3) and 2 wall thicknesses. The ventricular dimensions define the 3 axes of a nonprolate ellipsoid whose volume is calculated from the formula:

$$\text{volume} = 4/3\pi abc \tag{2}$$

where $a = L_1/2$, $b = L_2/2$, and $c = L_3/2$. A mean wall thickness is calculated by averaging the 2 available values.

All calculations are done on a PDP-12 computer using a paper tape input and teletype or plotter output. A computer plot of averaged dimension and volume data for 2 consecutive cardiac cycles is shown in Figure 5.

It should be emphasized that this method does not measure true left ventricular cavity volume; rather, since a rim of endocardial muscle includ-

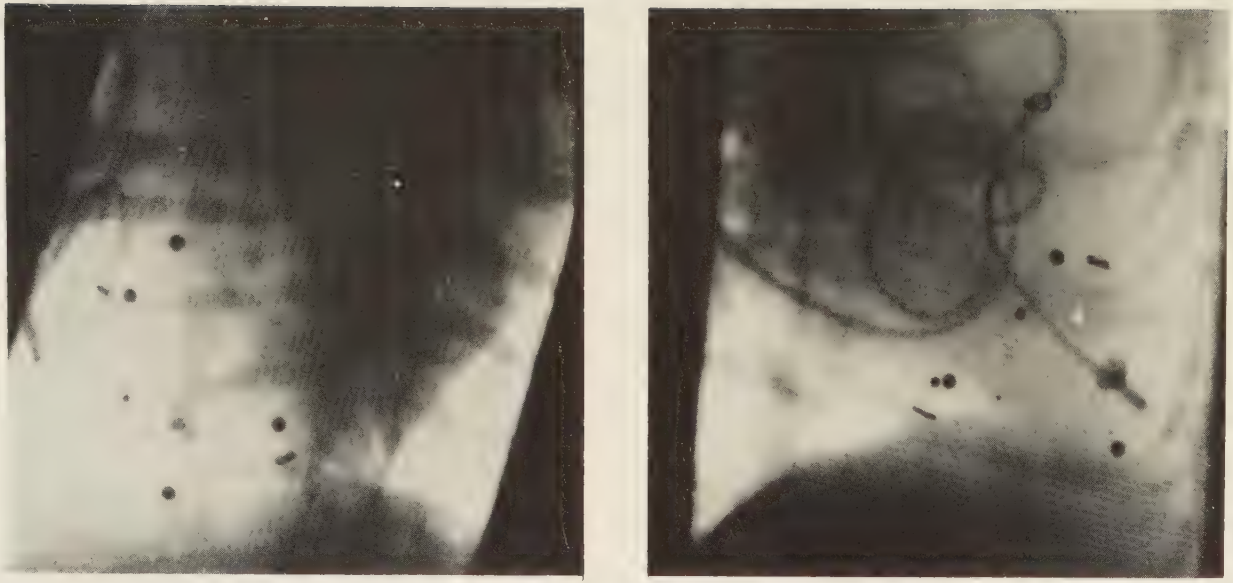

Fig. 4. Biplane x-ray exposures of the dimension markers in the left ventricle of a chronically instrumented dog. The left panel is the anterior-posterior view and the right panel is the lateral view. Also visible is an implanted left ventricular pressure transducer in the lower right corner in the right panel and aortic flow probe at the top of each panel. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

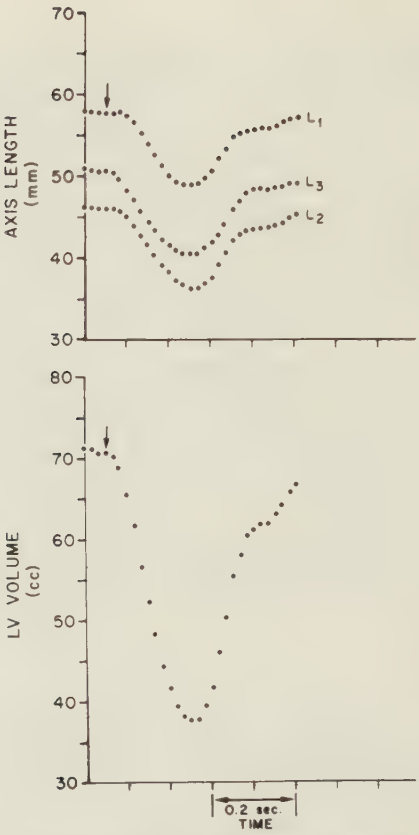

Fig. 5. A computer plot (points accentuated by artist) of the major axis (L_1) and two minor axes (L_2 and L_3) in the upper panel, and calculated ventricular volume in the lower panel. Averaged data from 2 consecutive beats are shown. The arrow indicates the point where the QRS of the electrocardiogram occurred. Reproduced, by permission, from the *Journal of Applied Physiology* 33:132, 1972.

ing the papillary muscles and trabeculae carneae lies between the beads and cavity, the distances and volumes calculated by this technique represent those of an idealized shell of left ventricular myocardium uninfluenced by the convolutions of the endocardial surface. However, considerable data suggest this technique does provide an accurate estimate of stroke volume and does follow instantaneous and beat-to-beat changes in ventricular volume. These data are considered in detail in a separate paper appearing elsewhere in this book. (11).

SUMMARY

A method for measuring three dimensions of the left ventricle utilizing chronically implanted radiopaque beads is described. The motion of the beads is followed with biplane cineradiographs taken at 60 fps. The absolute length of each axis can then be determined every 16.7 msec with left ventricular volume calculated by substitution of the axis lengths into the formulae for volume of an ellipsoid.

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34. SURGICAL IMPLANTATION OF ULTRASONIC GAUGES FOR MEASUREMENT OF LEFT VENTRICULAR INTERNAL TRANSVERSE DIAMETER[1]

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Estimation of changes in cardiac chamber size is essential for understanding cardiac function. Efforts to measure left ventricular volume by cardiometer (1), thermodilution or dye dilution (2), or x-ray techniques (3, 4) have been hampered by unphysiologic interventions, inaccuracy and, in the case of x-ray studies, tedious, expensive processes which are unsuitable for some conditions, particularly exercise.

Measurement of left ventricular transverse diameter with a sonocardiometer provides a technique for analysis of an important left ventricular dimension which is simple, continuous, requires a minimum of equipment and facilities, does not interfere with physiologic function, and is suitable for use in conscious animals in virtually any level of activity, including exercise. However, the initial studies by Rushmer and co-workers (5) used transducers affixed to the external surface of the left ventricle. Therefore, the interposition of the ventricular walls, which change in thickness during the cardiac cycle (6), precluded accurate determination of internal chamber dimensions. Measurement of internal left ventricular diameter with sonocardiometer transducers placed on the endocardial surface of the ventricle directly measures the diameter of the chambers and avoids errors due to wall thickness changes (7).

SURGICAL IMPLANTATION OF TRANSDUCERS

Dogs of at least 17 kg in weight are desirable. General anesthesia is obtained with pentothal alone or pentothal and methoxyfluorane. A left thoracotomy is performed in the fifth intercostal space. Umbilical tape

[1] The research described in this paper was supported, in part, by U.S. Public Health Service Grants HE-12415-01 and HE-14355-01 from the National Heart Institute.

occluders, made by drawing the ends of the umbilical tape through a 3-inch length of rubber tubing, are placed on the superior and inferior vena cava.

The pericardium is opened and two 2-0 atraumatic silk control stitches are placed just below and parallel to the first diagonal branch of the left anterior descending coronary artery (Fig. 1). The wires of one sonomicrometer transducer are threaded through the eye of a 4-inch needle made from 0.025-inch diameter stainless steel wire. The wires of a second transducer are passed through the lumen of a 5-inch length of 10-gauge stainless steel needle tubing.

The vena cavae are occluded to prevent excessive bleeding during implantation of the transducers. A stab incision is then made, with a #11 scalpel blade, through the ventricular wall between the two control stitches. The needle, with the first transducer attached, is thrust into the incision,

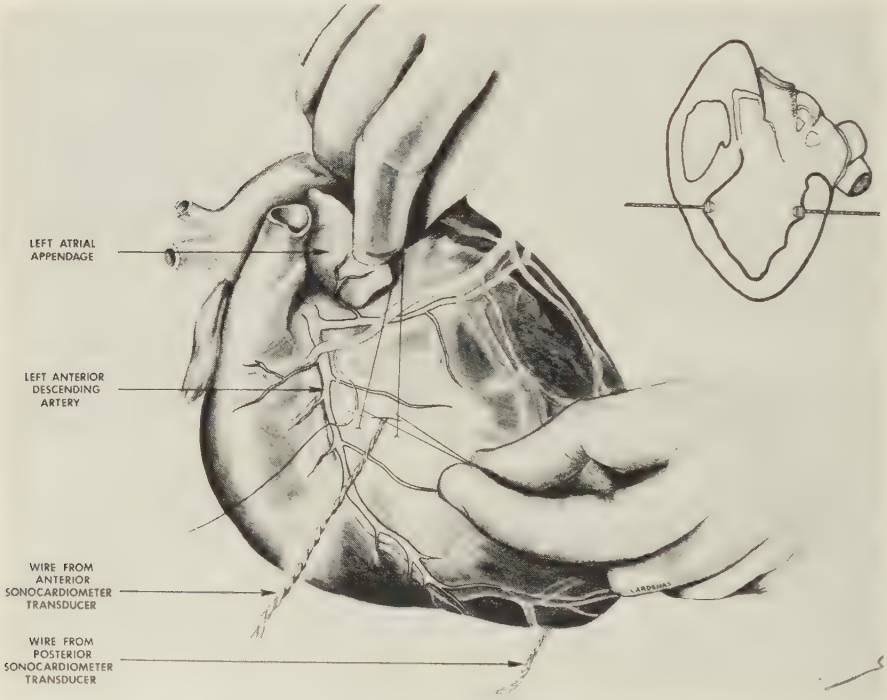
LEFT ATRIAL APPENDAGE
LEFT ANTERIOR DESCENDING ARTERY
WIRE FROM ANTERIOR SONOCARDIOMETER TRANSDUCER
WIRE FROM POSTERIOR SONOCARDIOMETER TRANSDUCER

Fig. 1. Bleeding is prevented by crossing holding sutures while wound is closed with continuous sutures. Insert at upper right is schematic showing position of the two implanted transducers, one on the anterior and the other on the posterior endocardial surface. Reproduced, by permission, from the *Journal of Applied Physiology* 24:1968.

allowed to traverse the ventricular cavity, and is then pushed through the posterior ventricular wall approximately 5 mm to the left of the posterior interventricular groove at the same transverse level as the incision on the anterior wall. The needle is pulled through the posterior wall and then, by exerting tension on the attached wires, the transducer is pulled through the anterior wall incision and positioned against the endocardial surface of the posterior wall.

The second transducer is then pushed through the incision and the tubing immediately withdrawn. The wires are gently pulled until the transducer is properly positioned against the endocardial surface of the anterior wall. An assistant controls bleeding by crossing the control sutures and applying traction to hold the edges of the wound together. The incision is closed with continuous stitches using 6-0 Tevdek suture. After the incision is closed, the venous occluders are released and both sets of transducer wires are anchored by stitches in the external surface of the ventricle. Interruption of venous inflow can be tolerated by the animal for up to 2 minutes; if this is not sufficient time in which to perform the implantation, bleeding can be avoided with the control sutures and direct digital pressure to the wound while the occluders are temporarily released, at any stage.

If desired, other instrumentation can be implanted during the same operation. We routinely place a flow probe around the ascending aorta and, using the venous occluders and control sutures to limit bleeding, a solid state pressure transducer (P17, Konigsberg Instruments Inc.) within the left ventricle through an incision on the anterior wall near the apex. A catheter placed in the left atrial appendage is frequently useful.

The wires of the sonocardiometer transducers and other instruments are run through the subcutaneous tissue and exteriorized at the back of the neck. Needles made from stainless steel rods about 10 inches long with 2 small holes drilled in the blunt end through which the wires are threaded can be used to quickly pass the wires to the neck.

We have successfully instrumented approximately 100 dogs with sonocardiometer transducers. The transducers function well for 2 to 3 months. Approximately 75% of implantation attempts yield satisfactory records.

Failures are occasionally due to creation of mitral insufficiency by striking papillary muscles or chordae tendineae. However, the most common cause of failure is malposition of the transducers so that the two piezoelectric crystals are not facing each other in the same horizontal plane. Records from malpositioned transducers are valueless for physiological interpretation since the complex geometry of left ventricular contraction does not allow differentiation of changes due to vertical or lateral wall movements from those due to transverse shortening. To avoid such error,

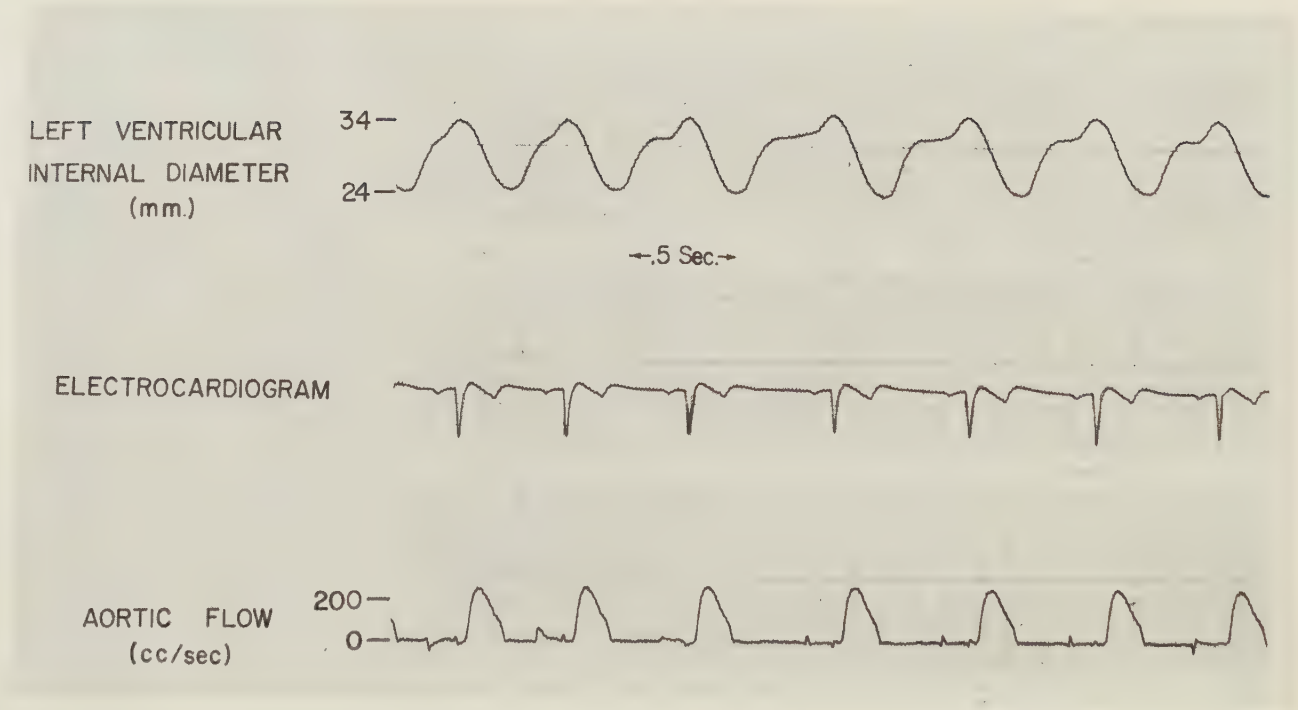

Fig. 2. Analog recording of simultaneous left ventricular internal transverse diameter, electrocardiogram, and pulsatile aortic flow in a conscious, resting dog. Reproduced, by permission, from the *Journal of Applied Physiology* 24:1968.

our electronic system is so designed that malpositioned crystals do not give recordings, allowing instant recognition of improper surgical placement. Careful postmortem examination is also performed to confirm proper placement.

RECORDING DIAMETER

Left ventricular transverse internal diameter is measured with the sonocardiometer designed by Stegall et al (8). The instrument measures transit time between the transducers as a simple DC bistable output directly equivalent to the absolute diameter. This output can be recorded on any standard laboratory recorder (Fig. 2). It is essential that the signals be carefully monitored with a high frequency oscilloscope during recordings to insure that the bistable is correctly tracking the transmit and receive signals. The system has functioned well through a wide range of states including rapid volume loading, high resting heart rates in vagal block or pacing, and exercise by swimming or running (9-11).

Virtually all our data have been accumulated in chronically instrumented animals, starting at least 10 days after surgery. We have found acute open chest recordings to be unsatisfactory because of abnormal ventricular function and recording artifact due to slight movements of the transducer. During the first several days after surgery the heart tends to be very small and responses to interventions are suboptimal. The primary value of this technique, therefore, is for 2-3 month studies of chronically instrumented, conscious animals rather than for acute studies, where the data may be unreliable.

SUMMARY

A simple, closed-heart technique for implantation of piezoelectric crystal transducers to provide a continuous recording of left ventricular internal transverse diameter is described.

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35. IMPLANTATION OF DIMENSION TRANSDUCERS

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To study dimension changes in chronic animal preparations without irreversibly altering the target organ, a variety of implantation techniques must be considered. For the study of veins (1, 2), for example, the transducer must be small and lightweight, and the suturing technique should produce a minimum of trauma (6-0 non-reactive suture on an atraumatic needle). We have used a small strip of Silastic sheet on the back of the transducer (Fig. 1) and sutured the overlapping ends of the strip to the vessel wall, leaving the vessel wall immediately under the transducer uninjured. This approach also reduces the chance of adhesions on the outer aspect of the transducer. Similarly, to measure venous distending pressures, a flat Silastic balloon is placed in close proximity to the vessel, and a Silastic catheter is advanced into the lumen, preferably from a venous branch. In the superior vena cava, we have used the azygos vein for cannulation.

Studies of cardiac dimensions present no special problems if external dimensions are satisfactory. However, for internal dimensions, placement may represent a severe challenge. If the transducer is inserted through a stab wound through the ventricular wall, the position of the transducer in relation to papillary muscles or to the circumference is uncertain. If the behavior of the myocardial wall itself is the target variable, the injury of the stab wound cannot be ignored, and there is a substantial risk that there may be a degree of physical tethering between the transmitter and receiver components of the transducer. To avoid these problems, it is possible to use cardiopulmonary bypass and to suture the transducers in the ventricle under direct vision. An alternative to the use of bypass technique is profound hypothermia.

Profound hypothermia was introduced into our institution by Dr. Henry Mohri, utilizing deep ether anesthesia and surface-induced cooling (3). When the core temperature reaches 20°C, up to 60 minutes of complete circulatory arrest is possible without detectable neurological injury. We use a cuffed endotracheal tube, a fixed-volume respirator, and a closed rebreathing circuit to which oxygen and small amounts of liquid ether are added.

The animal is placed on his back and submerged in ice water except for his head (Fig 2). Intravenous low molecular weight Dextran helps maintain cardiac output and prevent sludging. In sequence, the cavae are occluded, ventilation discontinued, and the aorta and pulmonary artery are clamped. Following placement of transducers via a left atrial incision, resuscitation is begun by re-establishing caval flow and respiration, and instituting gentle cardiac massage. Defibrillation may be needed, as well as replacement of blood losses. Rewarming is accomplished by surface means, with warm water at 40 to 42°C, until the core temperature has returned to 35°C. Post-operative care includes tube evacuation of air and blood, and other customary measures.

Fig. 1. Three transducers for chronic implantation. On the left, one of a pair of ultrasonic dimension transducers, with a dark acrylic acoustical lens, backed by a thin Silastic sheeting. In the center is one of a pair of endocardial ultrasonic dimension transducers, embedded in a small block of Silastic. On the right is an aortic flow probe for the pulsed ultrasonic flowmeter. Note the piezo-electric crystal at 12 o'clock on the bivalved probe, and the relatively thin walls and short length.

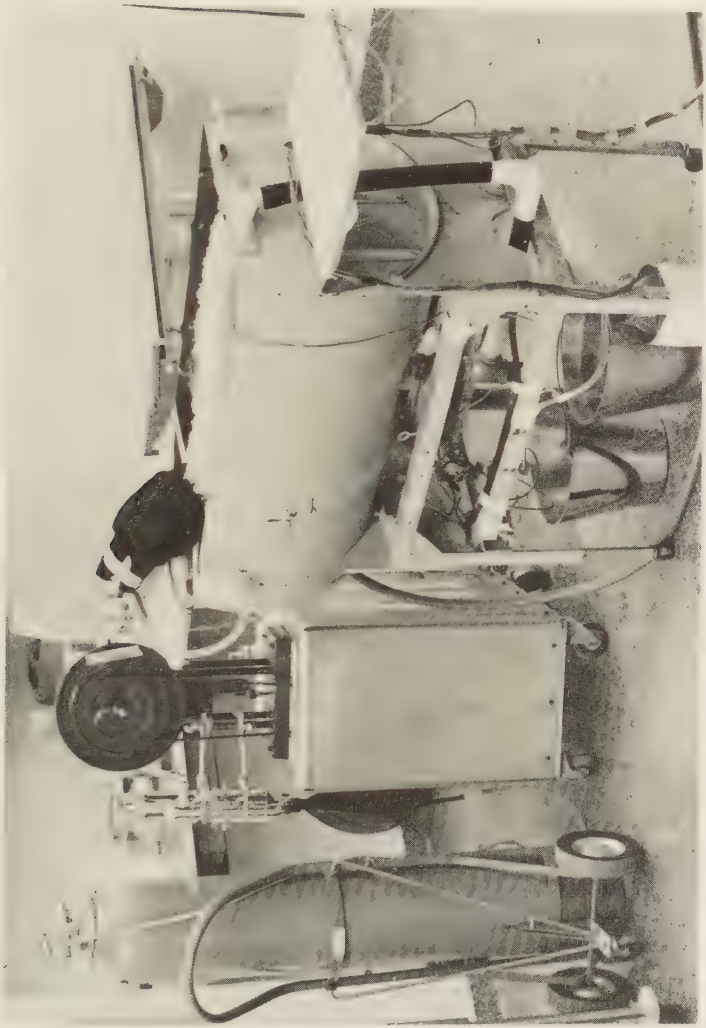

Fig. 2. Photograph of an anesthetized dog immersed in a tank of ice water. On the left is a Palmer respirator, with a closed inhalation system for ether-oxygen.

The mortality, in our experience, is greater than for simple thoracotomy, but the avoidance of physical injury to the target organ justifies the effort.

SUMMARY

Accurate recording of changes in dimension in chronic animal studies requires implantation techniques which minimize adhesions or injury to the target organ. Silastic sheets bonded to the outer surface of the transducers prevent excessive scarring of external surfaces of veins. Stab wounds may be avoided in studies of internal cardiac dimensions by a technique which permits visualization of the endocardial surface. "Open heart" techniques require either a pump-ventilator, or an innovative technique of profound hypothermia. The method uses deep ether anesthesia and surface cooling to 20°C. Up to 60 minutes of circulatory arrest is possible without neurological injury.

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36. THE IMPLANTATION OF MULTIPLE TRANSDUCERS IN THE THORAX[1]

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The important thing in considering multiple implants is the sequence with which the various procedures are to be carried out. In general all dissection that is required should be accomplished first; second, any procedure requiring the movement of the heart, and finally, any procedure that requires movement of the vessels only (1). The current section will illustrate some of these points using as an example the implantation of an electromagnetic flow probe around the ascending aorta and a multichannel telemetry unit containing three pressure transducers and electrocardiographic leads.

With the selection of the instrumentation having been accomplished for the experiment in question, the flow probes and the telemetry unit are placed in the container for cold sterilization. Several sizes of flow probes are placed in the container so that an appropriate size can be used at the time of surgery. The heart is approached through an incision in the left fifth intercostal space. The lungs are removed from the operative field by packing them in a moist towel. The pericardium is opened from the apex of the heart to the adhereance into the ascending aorta. This procedure is aided by using a wooden tongue depressor and an electrosurgical unit. This procedure decreases the bleeding from pericardial vessels. A cradle is made of the pericardium by placing sutures through it and attaching these sutures to either adjacent muscle layers or clamping them onto the wound drapes.

Dissection of the ascending aorta is accomplished first. Using either sutures or tissue forceps, the fat pad overlying the pulmonary artery and aorta is grasped and retracted toward the pulmonary artery. This puts tension on this tissue and allows one to visualize a cleavage plane between the two vessels. Using blunt and sharp dissection the area between the two vessels is separated, trying to leave as much of the fatty tissue on the pulmonary artery side of the dissection as possible. The fat pad covering the

[1] Supported, in part, by NASA Contract # NGR 44088002.

aorta is dissected from the vessel and removed. Care should be taken at this point since perforating arteries from the aorta into the fat pad are encountered in a large number of animals. If this occurs a curved mosquito hemostat can usually be used to obtain hemostasis. A right angle forcep is passed around the aorta starting between the aorta and pulmonary artery. The forcep is spread gently to increase the size of the opening between the two vessels. Now additional dissection can be accomplished on the lesser curvature of the aorta to mobilize the vessel. By using one's finger the posterior reflection of the pericardium on the aorta can be felt. This should be cut to obtain adequate dissection of this area. Following this dissection the aorta should be mobilized from the heart to the branches coming off the top of the arch. The most common point of trouble is the lesser curvature of the aorta; thus careful inspection should be made to insure that sufficient space is available for the flow probe.

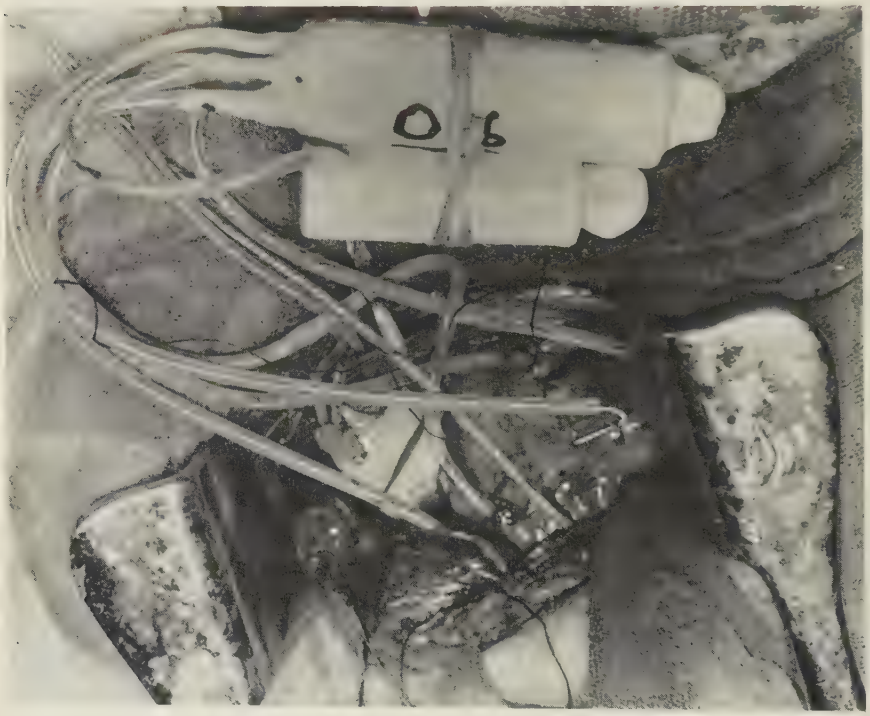

Fig. 1. Implantation of multiple transducers in the chest. Electromagnetic flow probe can be seen around the ascending aorta as well as the multichannel telemetry unit.

The implantable telemetry unit is removed from the sterilizing soulution and washed in saline thoroughly. It is brought into the operative field and the first pressure cell is placed in the left atrium as described in a previous section. The second pressure cell is implanted in the left ventricle through the apical dimple. The third pressure cell is implanted in the right ventricle near the pulmonary outflow tract. The procedure used for this pressure cell is the same as that described for the left ventricular pressure cell. One lead of the electrocardiographic electrode is sutured to the left ventricular free wall. These electrodes are made of spring wound stainless steel. The coils at the tip are pulled apart and a suture tied between one of the coils. The suture is then passed through the myocardium with a taper pointed needle. The second electrode is sutured to the chest wall in the same manner. The telemetry unit is placed in the posterior thoracic gutter over the diaphragm.

An umbilical tape is passed around the aorta to measure the circumference of this vessel. An appropriate size flow probe is selected following this. In our experience a flow probe slightly larger than the calculated diameter should be selected for use. The probe is washed in saline before use. The probe is placed around the aorta and fastened. The probe should be rotated on the aorta until the leads are protruding over the surface of the heart; this insures that the lead wires are not down between the aorta and pulmonary artery. Two pieces of Ivalon sponge, about 5 mm in width and long enough to encompass the aorta without constricting it, are moistened. One piece is pulled around the aorta between the heart and the probe. Using a length of 3-0 Tevdek suture, the needle is passed through one end of the sponge, through the adventitia of the aorta, the opposite end of the sponge and then back through both ends of the pieces of sponge. The suture is tied tightly. The same procedure is repeated for the second piece of sponge placed between the flow probe and the branches arising from the arch of the aorta. This wedges the probe between the two pieces of sponge and effectively prevents any movement of the probe. Dacron graft material has been used in a similar fashion but we have found that the sponge works better for us. Aortic rupture has been practically eliminated by this procedure. The lead wires are brought out of the chest and sewed to muscle layers making sure that a small loop of lead wire is left in the chest cavity.

The incision is closed and the chest evacuated after full expansion of the lungs.

SUMMARY

Multiple transducers have been implanted in the chest of dogs, baboons, and chimpanzees. In each of these animals, thought must be given to the sequence of implantation prior to the actual surgery. This approach will prevent undue delays and insure success of the surgery. The implantable unit used in these studies has functioned well for over a year and has presented no serious problems from the presence of a foreign mass in the chest. A foreign body reaction of tissue encapsulation occurs around each unit and, in general, precludes the replacement of the battery pack. Care must be exercised concerning the placement of the pack in the chest. We have found the posterior thoracic gutter to be a good location.

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37. MULTIPLE IMPLANTS IN THE CHRONICALLY INSTRUMENTED DOG[1]

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INTRODUCTION

Two decades ago, Rushmer pointed out the considerable differences in quality of data acquired from the conscious instrumented dog and that acquired from the classical open-chested, anesthetized animal. He demonstrated the depressant effects of anesthesia, thoracotomy and artificial respiration on cardiac function (1).

There was considerable controversy over concepts derived from experiments conducted in the classical open-chested dog which were not directly transferrable to conscious animals. For, although a given hypothetical control mechanism may be clearly demonstrable in the controlled experiment in anesthetized dogs, it may be completely absent as a normal control mechanism in the conscious animal. In addition, the work of Hawthorne (2, 3) has repeatedly pointed out that the dynamic geometric changes occurring during cardiac contraction and relaxation in conscious, instrumented dogs are significantly different from those seen in the classical preparation.

Over the past two decades, the professional cardiovascular physiologist has concluded that the conscious instrumented animal is the experimental preparation of choice for the study of cardiovascular function. The significant development forcing this conclusion was the marked technological advancement making studies in conscious animals possible. These advances included the development of pressure transducers of the catheter tip and, more recently, of the implantable type; both have excellent operational characteristics. These characteristics include long term stability and a frequency response which is adequate for the system under study. In addition, there was the development of implantable electromagnetic flow meters allowing monitoring of beat to beat changes in stroke volume from con-

[1] Supported, in part, by NIH Grant HE-01015-20.

scious animals. Further, there have been numerous approaches to measurement of dimensional changes in the left ventricle. These include sonocardiometry by Rushmer and co-workers (4) and Bishop and co-workers (5) and biplane cinefluorography by Mitchell and his associates (6), using the implantation of lead beads at the subendocardial layer. The method of inductance micrometry has been developed in our laboratory over the past twenty years for the measurement of left ventricular diameter (7), cross sectional area and left ventricular length (8), and wall thickness (9). This method has been used by other investigators as well. Wilson and his associates (10) have measured left ventricular transverse dimension; Davila and co-workers (11) used the same approach for the estimation of cross sectional area of the left ventricle and estimation of volume.

It has been the aim of our laboratory to measure the minimum number of primary variables in conscious animals compatible with long term survival of the animal and with maximum evaluation of cardiac performance. This task requires the measurement of simultaneous changes in left ventricular internal and external diameter, in the midplane of the left ventricle, normal to its long axis. In addition, changes in left ventricular, left atrial, and aortic pressures provide a "built in" source of systematic forcing functions for the system. Figure 1 shows the relative placement of the gauges used for the measurement of the primary variables listed above which are taken from the left ventricle of the conscious dog. The black dots shown represent the position of lead markers in the subendocardium for demarcating the shell of the internal volume of the left ventricle according to the methods of Mitchell and co-workers (6). Through the simultaneous use of analog and biplane cinefluorographic techniques, it is possible to cross calibrate at least these two methods for volume and dimensional measurement. The distance between coils "B" and "B′ " represent the left ventricular internal diameter; the distance between coils "A" and "A′ " represent the left ventricular external diameter in the same plane. The relative positions of the pressure cells (Konigsberg Instruments, Inc.) are shown in the left ventricle, left atrium, and aorta. The lines labeled L. Atrial Stim. and L. Vent. Stim. represent the placement of multi-stranded, stainless steel electrodes in the atrial and ventricular myocardium for the purposes of stimulation and recording. Studies in our laboratory and in conjunction with Mitchell (8) showed that during ejection, the internal axis ratio changes less than 4%. From the primary variables monitored, numerous derived variables can be obtained which are useful in the assessment of cardiac performance.

METHODS

Inductance micrometry is based on the principle that when a closed conductive loop of fixed cross-sectional area is placed in a magnetic field, an

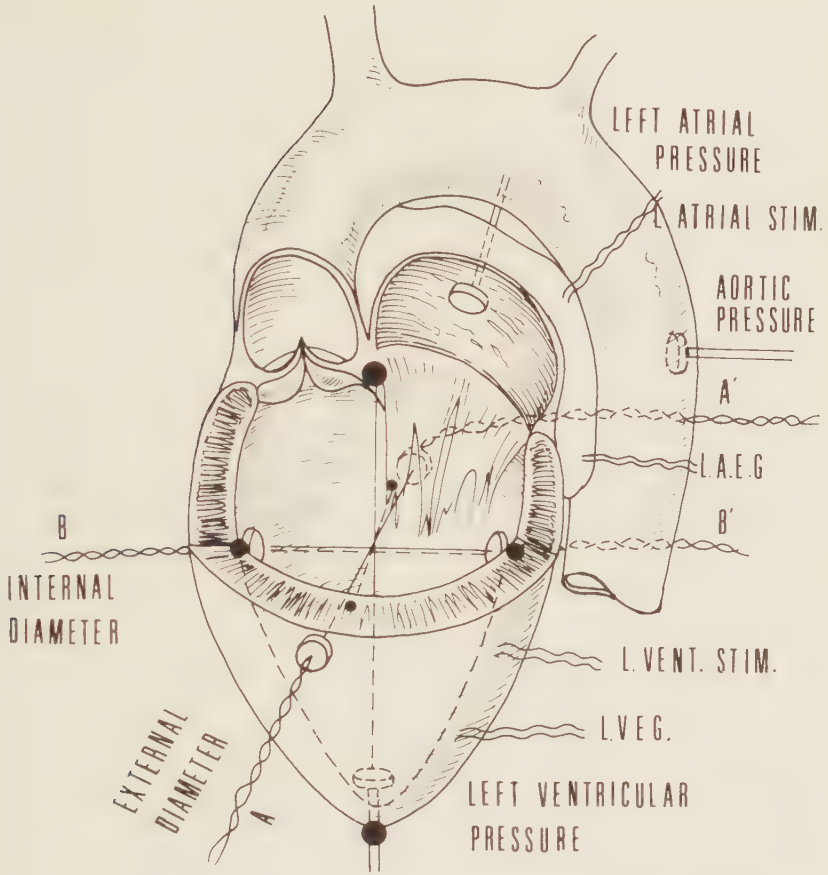

Fig. 1. Diagram showing the relative placement of internal and external diameter gages and pressure transducers in the left ventricle (see text).

electromotive force (EMF) is induced in the loop. This EMF is dependent on the distance separating the loop from the magnetic field. The principal limitation of the application of this method is the inherent non-linearity between output voltage and separation for such a system. In this system, two small, specially constructed wire-wound coils (Hazen Everett Co., 282 Island Rd., Mahwah, New Jersey 97430) are placed on the endocardium. One coil, (B), the primary coil, is excited at a known frequency and voltage for generation of a magnetic field. The second coil, (B'), placed diametri-

cally opposite to, and coaxial with, the primary coil, has an induced electromagnetic force which is a linear function of the distance separating the primary and secondary coils. Each coil weighs approximately 500 mgs, and is 6 mm in diameter and 3 mm in thickness. A system designed in our laboratory provides all the electronic functions necessary to deliver the driver power, linearize and amplify the dimension signal, and calibrate the output from the inductance micrometers (13). The output from that system is shown in Figure 2. This diagram shows that the voltage output is a linear function of the spatial distance between the two coils over this range in LVID.

PLACEMENT OF LVID COILS

The problem is placement of two coils in a plane normal to the major axis of the left ventricle on its internal surface without significant blood loss and without entanglement of gauging devices in intracardiac structures such as chordae tendineae or papillary muscles. The technique described below allows for accomplishment of this task. Adequate placement of the coils

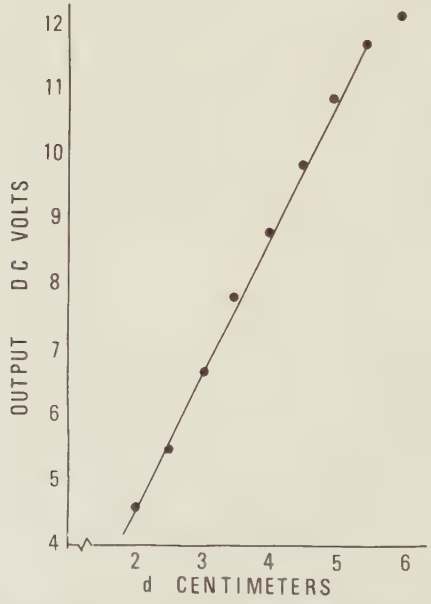

Fig. 2. Linearized transfer function of the inductance micrometer system showing output voltage versus coil separation.

requires special attention to the anatomy of the coronary arteries. On the anterior surface, the second branch of the left anterior descending coronary artery is used as a landmark for the point of entry into the ventricle. A point in the same plane on the posterior surface, close to the posterior descending coronary artery, locates the site of exit from the ventricle. A purse string suture (4-0 Tycron) is placed at each of the selected points. Two silk sutures are placed at the apex for the purpose of manipulating the ventricle and for hemostasis after ventriculotomy. A 2-0 silk ligature (30 cm long) is attached to a thin stainless steel stylus. The path of the left ventricular internal diameter is demarcated by passing the stylus into the point of entry and out the site of exit on the posterior surface (Fig. 3, step 1 and 2). The stylus is removed and the ends of the ligature secured with fine hemostats. The first assistant to the surgeon then applies tension to the ligature and draws it taut. The surgeon then makes a ventriculotomy at the apical dimple and controls bleeding with his thumb. He then passes a specially constructed snare into the ventricle to capture the ligature being held taut by his assistant (step 3). When he captures the ligature, the assistant releases it, and it is pulled out of the ventricle (step 4). One purse string at the apex is then closed in order to control bleeding. The ligature is cut in the middle; each free end is then tied to a lead wire on one coil (step 5). Each coil is then drawn in place using its respective ligature (step 6), and the apex is repaired to prevent further blood loss. The purse string sutures are then secured about the leads from the coil on both the anterior and posterior surfaces of the left ventricle. At this point, the leads from the coils are connected and the diameter trace is monitored or recorded to check for contour and calibration, or checked with the finger to be sure of placement of the coil. It has been our experience that when the coils are placed either through papillary muscles, or entangled in chordae tendineae, or are measuring a chord length, several observations can be made: (1) the contour is bizzare, and (2) the calibration falls below the range or above the range of change for the gauge.

MEASUREMENT OF LEFT VENTRICULAR EXTERNAL DIAMETER

The method of inductance micrometry is also used to monitor changes in left ventricular external diameter. The system used for this purpose is identical except for the frequency of excitation of the primary external diameter coil. These coils are similarly constructed and placed on the external surface in the same plane as the left ventricular internal diameter coils.

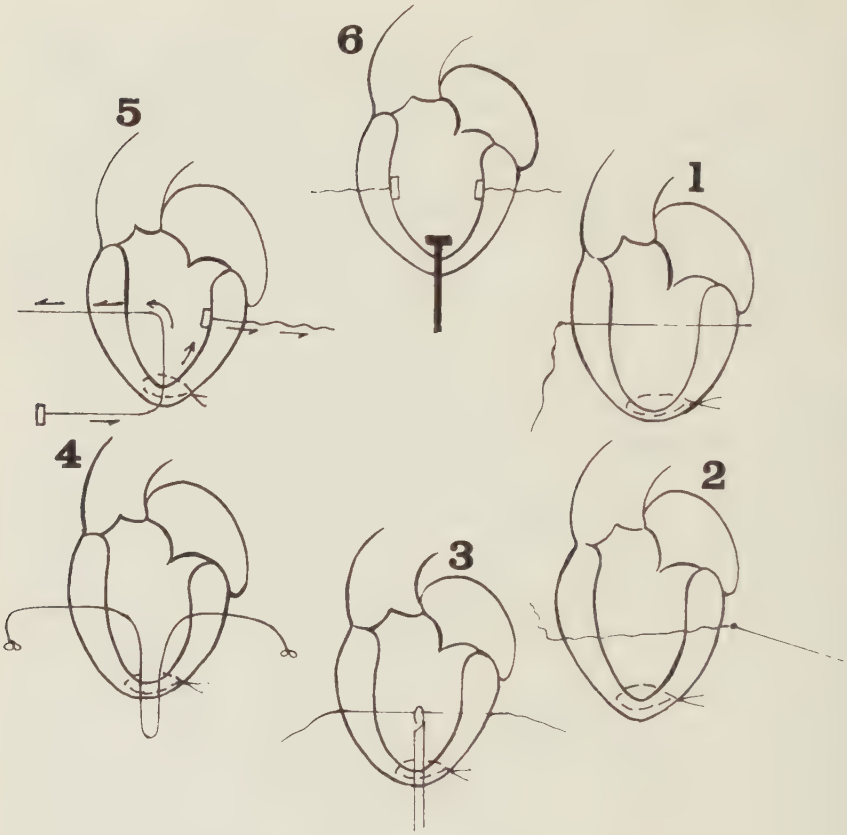

Fig. 3. Procedure for sugically implanting transducers (see text).

IMPLANTATION OF PRESSURE CELLS

In all dogs, measurements are made of left ventricular, atrial and aortic pressures with implantable pressure cells (P-20, 6.5 mm and 7.0 mm in diameter, Konigsberg Instruments Inc.) The implantable left ventricular pressure cell is usually placed at the time of internal diameter coil implantation. The cell is inserted into position through the apical dimple (Fig. 3, step 6). The aortic pressure cell is then implanted directly into the aorta, one centimeter distal to the subclavian artery. A 2 cm segment of the aorta is isolated from the surrounding pleura and a purse string suture (4-0) is placed in the adventitia at the site of implantation. The aorta is partially

occluded using a "J" shaped vascular clamp, aortotomy is performed at that site, and the cell is placed into the aorta. The cell is secured by closing the purse string suture around the lead from the cell. After complete hemostasis is established at that site, a Dacron sleeve placed around the aorta secures the cell and protects against future rupture of the aorta at the site of implantation. In order to implant the pressure cell in the left atrium, a purse string suture is placed in the body of the left atrium. A tangential anastamosis clamp is used to partially occlude the body of the atrium. An atriotomy is made within the purse string and the pressure cell is inserted. The clamp is removed and all air is displaced from the atrium by blood. The purse string suture is then closed and the cell is secured. The site of implantation is then reinforced with a one centimeter square Dacron patch.

After all gauges and other devices are implanted in and on the left ventricle and aorta, the entire chest cavity is repeatedly lavaged with sterile saline and complete hemostasis established. The pericardial space is cleansed and dried. The pericardium is closed with interrupted 3-0 silk sutures approximately 1.5 cm apart. All lead wires are positioned in the chest cavity so as not to stress the heart or the gauging devices. These leads are then brought out through the third intercostal space on the left side. Purse string suture closure of the site prevents pneumothorax. The lead wires are brought out through a subscapular route with the point of exit through the skin on the dorsal aspect of the neck. A small perforated tube is placed in the chest cavity in the dependent area such that when the animal is in standing position, drainage can be accomplished from both sides of the chest cavity. This tube can then be used for continuous drainage from the chest. The lungs are inflated under positive pressure to remove all areas of atelectasis. The ribs are approximated by interrupted double stranded (1-0) Mersilene sutures. The chest wall is closed in layers up to and including the skin.

POST-OPERATIVE CARE

The critical step in preparation of the chronic animals for studies of these type is that of post-operative care. This problem is discussed at length in another section of this Symposium. However, a few notes will be made here in relation to the preparation described in this report. First, we have used a small perforated tube for closed-chest water-seal drainage from the thoracic cavity. This tube is left in the chest cavity for 15 post-operative days. We have found that the mortality from pneumothorax and hydrothorax is reduced considerably because one can drain fluid daily and therefore minimize pulmonary atelectasis. Second, administration of antibiotics

for 15 post-operative days appears to be critical for survival of our animals. Third, because of the necessity of gauge implantation directly into the myocardium, for the first 72 hours the animal is vulnerable to the problems of ventricular tachycardia and premature ventricular contractions which can degrade to ventricular fibrillation and death during this period. In order to prevent this problem, we administer 200 mgs of Lidocaine HCl, i. m., each 12 hours for the first 72 hours post operatively. This protocol has significantly reduced our mortality in such animals.

REPRESENTATIVE RESULTS

A typical calibrated record from the conscious instrumented dog is shown in Figure 4. This record was taken from a dog on the twenty-fourth post-operative day. The animal was in good health as evidenced by temperature, respiratory rate, and body weight stability. The variables recorded, from the bottom to top, are (1) left ventricular electrogram (LVEG), (2) left ventricular external diameter (LVED), (3) left ventricular internal diameter (LVID), (4) left atrial pressure (LAP), (5) left ventricular pressure (LVP), (6) aortic pressure (AP), (7) the first derivative of ventricular pressure with respect to time (dP/dt), (8) intrathoracic pressure (ITP), and time (t). These variables represent the primary and preprocessed data (dP/dt) generally recorded on a given animal for study of cardiovascular function.

The finding of marked sinus arrhythmia is characteristic of the conscious instrumented dog in good health. The recording shows the variation in cardiac cycle length with the changes in intrathoracic pressure during the normal respiratory cycle. The stability and quality of the record shown is representative for the conscious instrumented dog. LVED and LVID can be seen to decrease during isovolumic contraction. However, the dominant dimensional change occurring in the plane of the minor axis is a marked decrease in internal and external diameter.

The reliability of use of simultaneous change in external and internal diameter for the purpose of estimating changes in wall thickness in the plane of the minor axis is shown in figure 5. This figure is a plot of the simultaneous changes in left ventricular pressure, with LVED and LVID at the same sensitivity, and the resultant calculated wall thickness and average meridional stress (12) in the plane of the minor axis with respect to time. The left ventricular wall thickness (closed squares) equals one-half the difference between LVED and LVID. The changes for wall thickness and average meridional stress (open squares) are plotted only for the period of ejection. It is of interest that the magnitudes of change and the time course of these two variables in the conscious dog are similar to the direct record-

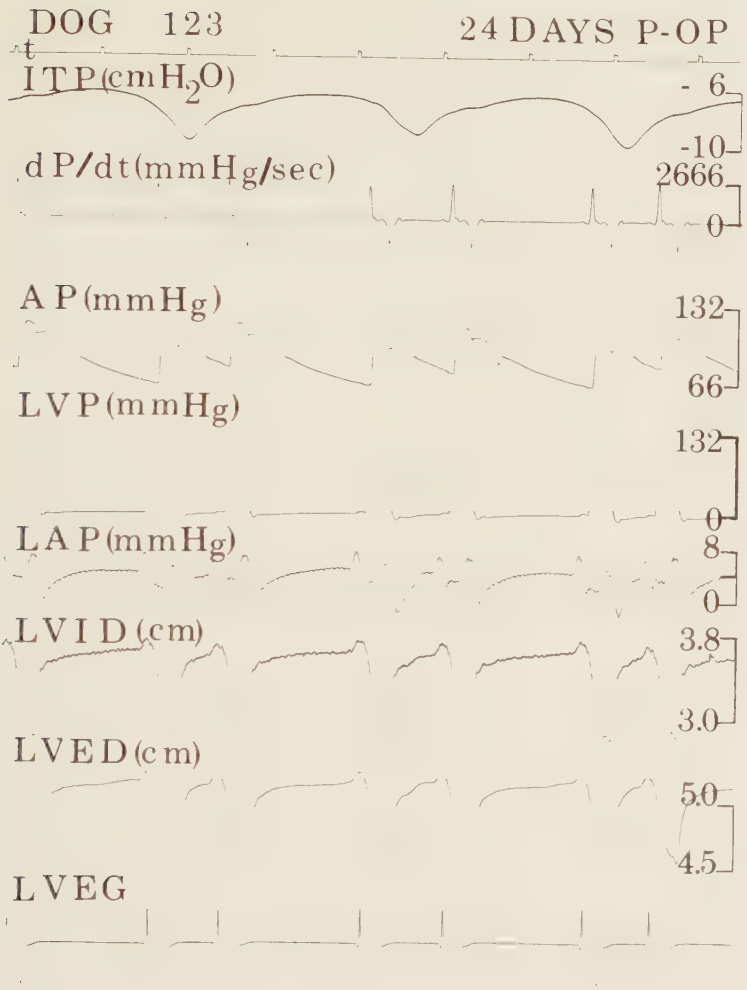

Fig. 4. Typical recording. From bottom to top, left ventricular electrogram (LVEG), left ventricular external diameter (LVED), left ventricular internal diameter (LVID), left atrial pressure (LAP), left ventricular pressure (LVP), aortic pressure (AP), dP/dt, and intrathoracic pressure (ITP), from a conscious dog.

ings of these variables, as previously reported (9, 12). That is, during the ejection phase the derived wall thickness (LVWT) shows a continuous increase with no change in LVP, and continued decrease in average meridional stress.

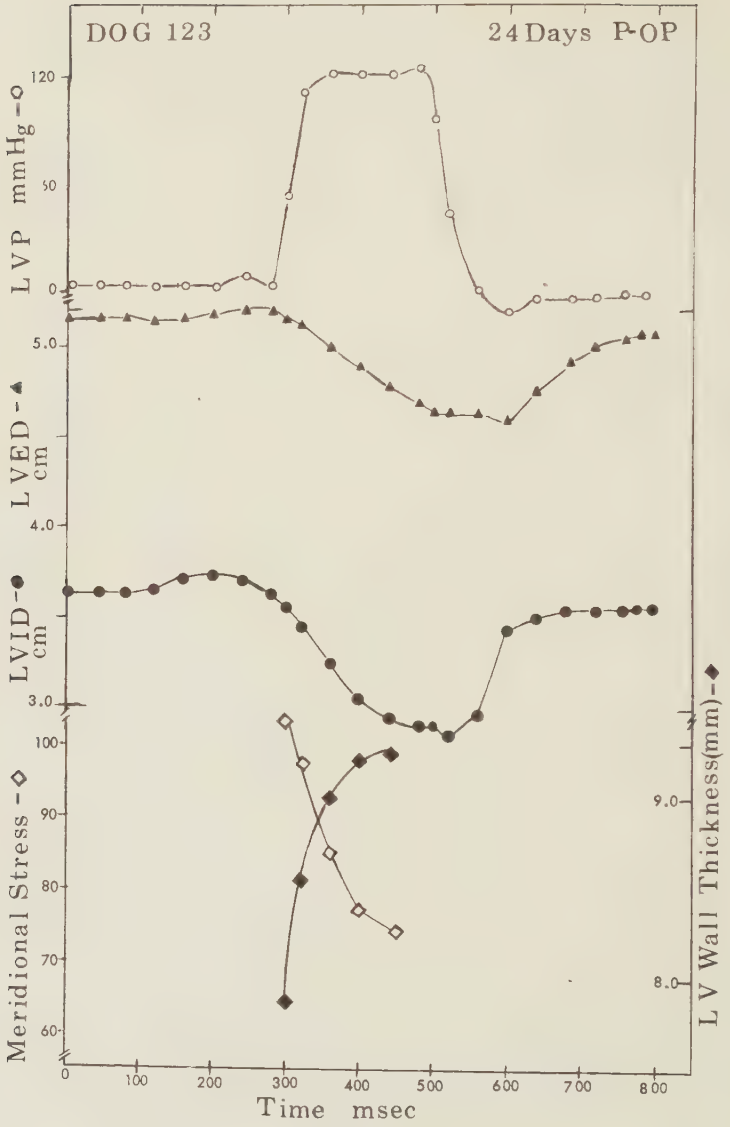

Fig. 5. A plot of the simultaneous changes in left ventricular internal and external diameter at the same sensitivity, along with left ventricular pressure. The changes in wall thickness and calculated meridional stress, occuring during the phase of ejection, are also shown.

SUMMARY

The guiding principle for multiple implantation is measurement of the minimum number of primary variables compatible with both long-term survival and maximum evaluation of the system under examination. This report outlines principles and procedures for placement of coils to measure left ventricular internal and external diameters, and transducers to measure ventricular, aortic, and left atrial pressures; representative results are shown. These animals have survived routinely up to six months, and one dog lasted eleven months. From the primary data recorded in such animals, numerous useful variables can be derived for study of myocardial performance in various experimental models.

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38. LEFT VENTRICULAR INTERNAL DIAMETER, PRESSURE, AND FLOW MEASUREMENTS IN CONSCIOUS DOGS: AN EVALUATION[1]

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Cardiac function can best be assessed by considering the left ventricle's performance both as a pump and as a contracting muscle. We approach such an evaluation through three basic physical measurements: diameter, pressure, and flow. The capacity of any pump can be expressed by its flow output and the pressure head it can attain, but the unique problems of the cardiac pump also require evaluation of muscle performance through simultaneous determination of an appropriate left ventricular dimension.

As described elsewhere (1, 2), we measure left ventricular internal transverse diameter with sonomicrometer transducers on the endocardial surface of the anterior and posterior walls of the chamber. At the same time a solid state, high fidelity pressure transducer (Konigsberg Instruments, Inc.) is implanted within the ventricle and an electromagnetic flow probe (Zepeda Inst., Seattle, Washington) is affixed around the ascending aorta. A catheter is implanted in the left atrium to furnish a check on zero drift of the solid state pressure transducer.

CALIBRATION OF THE FLOW TRANSDUCERS

Normally, all flow probes are calibrated prior to and following implantation. During implantation, the flow probes are checked in vivo by indicator dilution measurements. In all cases the in vivo and in vitro calibrations agree within the experimental error of the procedure used (±5%).

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CALIBRATION OF THE PRESSURE TRANSDUCERS

The Konigsberg pressure transducer is calibrated in a pressure bottle at various temperatures before implantation, and the calibration is checked upon removal from the animal. On occasion, the sensitivity of the pressure cell is checked in vivo by using a catheter manometer system (Statham P23Db).

In a normally functioning cell, in vivo and in vitro sensitivity calibrations are identical. However, zero drift does occur with all implanted pressure cells. Rather than catheterizing the animal during each experimental procedure for the identification of the absolute zero reference of the pressure cell, we equate the resting LVEDP to the MLAP as obtained from the left atrial catheter. The relationship between MLAP and LVEDP is a line of 45° passing through the origin (Fig. 1). Thus, MLAP and LVEDP are normally equal over the selected range. Others have also reported that the

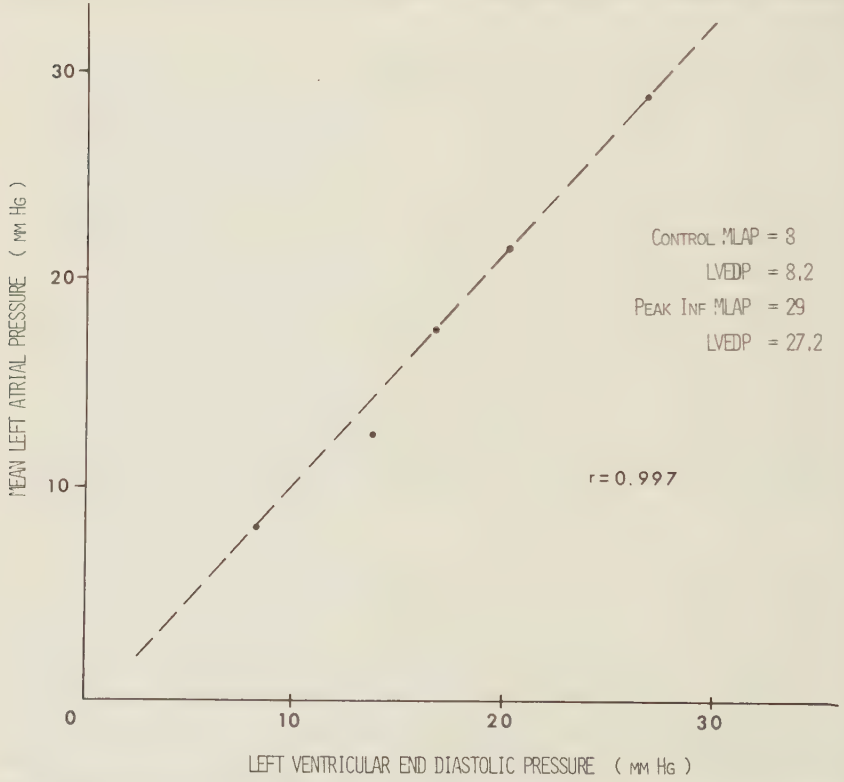

Fig. 1. Relationship between mean left atrial pressure and left ventricular end diastolic pressure.

resting pressures are sufficiently equivalent to permit use of this reference technique (3).

EVALUATION AND USE

Analyses of the utility of the transverse diameter recordings have been made in conscious animals under a variety of stresses which include pharmacological agents, acute volume loading, and exercise (2, 4, 5). In all of the cases we have found an approximately linear relationship between the instantaneous volume ejected and the transverse internal diameter during systole (Fig. 2) (6). Statistical analysis of the data showed that a linear relationship always described the data closely. Originally, we had hoped that a statistical fit which matched one of the accepted geometrical models could be obtained. If one used a quadratic fit ($y = a+bx+cx^2$), the equation was only good over the range of the data. A new fit was required if the size of the heart was altered. Thus, little information as to the functional relationship between these two variables was provided by this type of mathematical fit. A linear fit, however, provided us with a functional relationship which was applicable in all situations. In a few cases where the quadratic fit appeared to be more significant than a linear fit, both equations provided us with the same result when applied to the data. This was because the linear term of the quadratic equation was many times more significant than the quadratic term. To appreciate a linear fit, one must realize that a quadratic function is essentially linear over a very small segment (as long as *c* is very small), and the diameter changes during systole represent such a segment.

To evaluate further the utility of the transverse internal diameter as an index of left ventricular volume, we investigated the possibility that ventricular volume might be estimated from the transverse internal diameter measurement. We made this evaluation by calculating left ventricular volumes in animals previously instrumented with sonomicrometers and aortic flowmeters. Ventricular volume was estimated from the volume ejected and the transverse internal diameter. These volumes were compared to those obtained by thermodilution techniques (7, 8). Estimation of ventricular volume from the transverse internal diameter and volume ejected were obtained from the following relationships:

$$EDV = SV/1\text{-}ESV/EDV \quad (1)$$

where . . . . . EDV = the end diastolic volume,
ESV = the end systolic volume.

The EDV and ESV are equal to $GL_D D^2$ and $GL_S D^2$ respectively. G equals some constant geometrical fraction; L_D and L_S are the base-to-apex length during diastole and systole. Substituting these values into equation 1, the

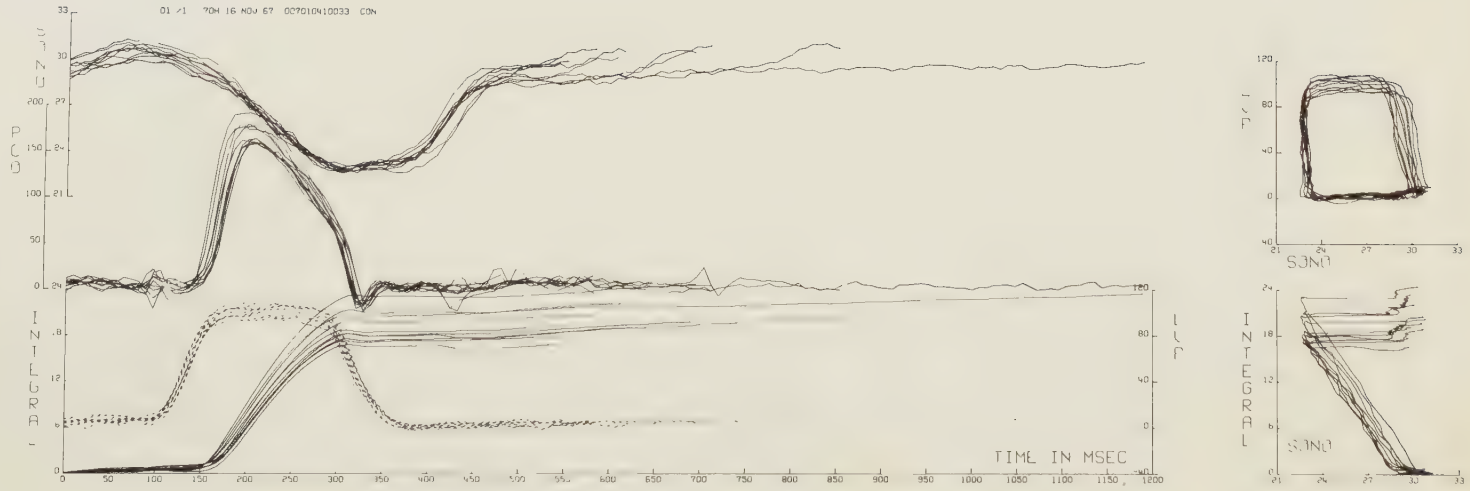

Fig. 2. Computer print-out of 10 consecutive heart beats. The traces to the right are left ventricular pressure plotted as a function of diameter (upper) and integral flow versus left ventricular internal diameter (lower). Reproduced, by permission, from *Cardiovascular Research* 6:163, 1972.

following relationship is obtained:

$$EDV = SV/\ 1\text{-}GL_S D_S^2 / GL_D D_D^2 \qquad (2)$$

Based upon the work of Feigl, et al (9), the base-to-apex length decreases approximately 10% during contraction. Therefore, $L_S = .9\ L_D$ and equation 1 becomes

$$EDV = SV/1\text{-}\left[0.9\ \frac{D_S^2}{D_D^2}\right] \qquad (3)$$

The validity of this equation is not affected if the transducers are placed across a chord rather than a true diameter as long as the transducers are in the same transverse plane. If a symmetrical contraction occurs, the ratio of the true end-diastolic diameter to the true end-systolic diameter is equal to the ratio of the measured end-systolic and end-diastolic diameters. The end-diastolic volumes calculated from the above relationships were 61% of those obtained from the thermodilution technique. It is well known that thermodilution techniques overestimate the actual volume (7, 8). More important is the fact that the residual fractions calculated from the transverse internal diameter measurements were less than those previously reported by angiocardiographic technique. Angiography tends to underestimate end-systolic volume while end-diastolic volume is reasonably accurate (10). Thus, it appears that the volumes calculated from the transverse internal diameter are somewhere near the true left ventricular volume and compare favorably with those reported using other techniques. We admit that many assumptions are necessary for the estimation of ventricular volume from a single dimension, but the utility of the transverse internal diameter is not dependent upon the fact that a ventricular volume can be estimated from the measurement, but rather that it is a good index of changes in left ventricular muscle fiber length. That the changes reflect changes in ventricular volume are readily apparent from the linear relationship between left ventricular stroke volume and transverse internal diameter during systole.

The stimulus for determining left ventricular volume has been the need for analyzing the heart as a pump as well as a muscular organ, since parameters such as end-diastolic fiber length, circumferential fiber shortening rate, and ventricular wall tension are used in evaluating performance of the heart as a muscle. Thus, definition of left ventricular volume has often been a means rather than an end since volun e is usually sought for the derivation of certain critical dimensions based on some assumed volume. A volume is

estimated using an approximate geometrical model, and then the dimensions corresponding to the volume and geometry are derived.

In most studies of cardiac muscle mechanics, the left ventricular cavity has been assumed to be a sphere, the volume of which may be determined by indicator dilution, biplane cineangiography or postmortem preparations. The velocity of shortening of the contractile element, circumferential shortening rate, and wall tension are then calculated from the diameter of a sphere corresponding to the determined volume. Measurement of the instantaneous transverse internal diameter of the left ventricle, as described in this study, eliminates these assumptions and approximations and allows the determination of many cardiac muscle parameters from actual measurements in the most important plane of contraction.

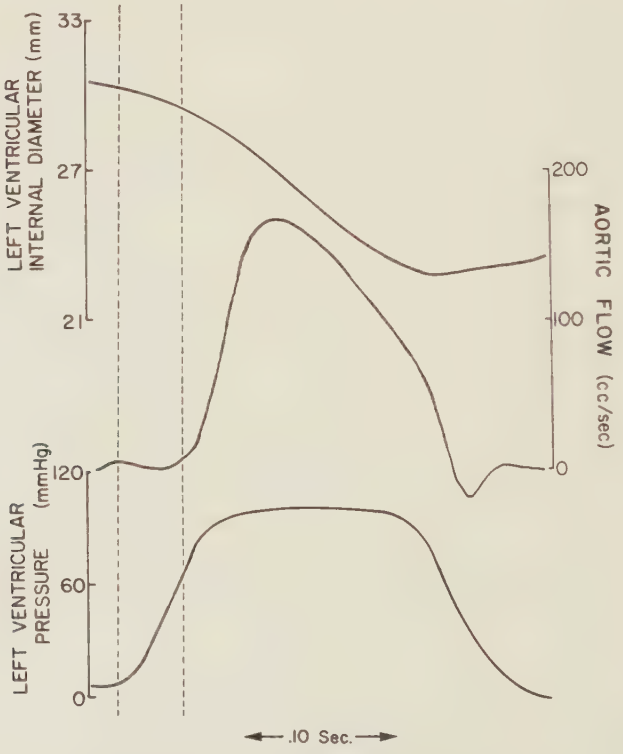

Fig. 3. Time relationship between left ventricular transverse internal diameter and left ventricular pressure. Reproduced, by permission, from the *Journal of Applied Physiology* 24:738, 1968.

In conscious animal studies in our laboratory, left ventricular transverse internal diameter, left ventricular pressure, and stroke volume are routinely measured. From these measurements we evaluate left ventricular function in terms of volume ejected and internal diameter relationships, and left ventricular pressure and diameter loops. In addition, we evaluate the first derivative of pressure and diameter. We have found that left ventricular muscle performance can be analyzed from the relationship between the stroke volume and diameter. This relationship allows us to evaluate the heart as a pump in terms of the extent of cardiac muscle fiber shortening. When animals are subjected to various stresses, the adaptation of the left ventricle can be assessed in terms of the Starling effect and the left ventricular systolic reserve (potential extent of cardiac muscle fiber shortening) (Figs. 2, 3).

A final point with regard to the time relationship between left ventricular transverse internal diameter, pressure and flow should be made (Figs. 3, 4). In all of our studies, shortening of the transverse internal diameter occurs during the isovolumic phase of left ventricular internal diameter (Figs. 3, 4). The degree of shortening during the isovolumic phase varies depending upon the stresses being imposed upon the animal, but at rest, the average total decrease in diameter occurring before ejection is 11%. Possible causes of the internal diameter change prior to ejection are accumulation of blood in the mitral valve region, where the highly elastic valves may bulge toward the atrium as the left ventricular pressure exceeds the atrial pressure, or a segmental contraction pattern with some portions of the ventricle contracting before others. Regardless of the cause, left ventricular fiber shortening does occur during the "isovolumic" portion of systole. This obviously limits the application of certain analyses of cardiac muscle mechanics which are often performed during this phase of the cardiac cycle.

A phase shift between the pressure, diameter and flow recordings cannot explain this observation. Both the pressure and flow recording techniques have excellent inherent frequency response. The Zepeda electromagnetic flowmeter uses the 400 cycle chopper of the Beckman Offner Oscillograph; thus the flow recordings are limited by the pen response of the recorder which is flat to 40 Hz. The frequency response of the Konigsberg solid state pressure transducer also exceeds the frequency response of the Beckman recorder. A Fourier analysis of the diameter measurement has demonstrated that the important frequency components are limited to 5 Hz. Thus, as compared to the flow and pressure measurement, changes in diameter are a rather slow process. On the other hand, the sonomicrometer has a phase lag of 40° at 20 Hz. Phase analyses of flow, pressure and diameter measurements have demonstrated that the diameter may lag the

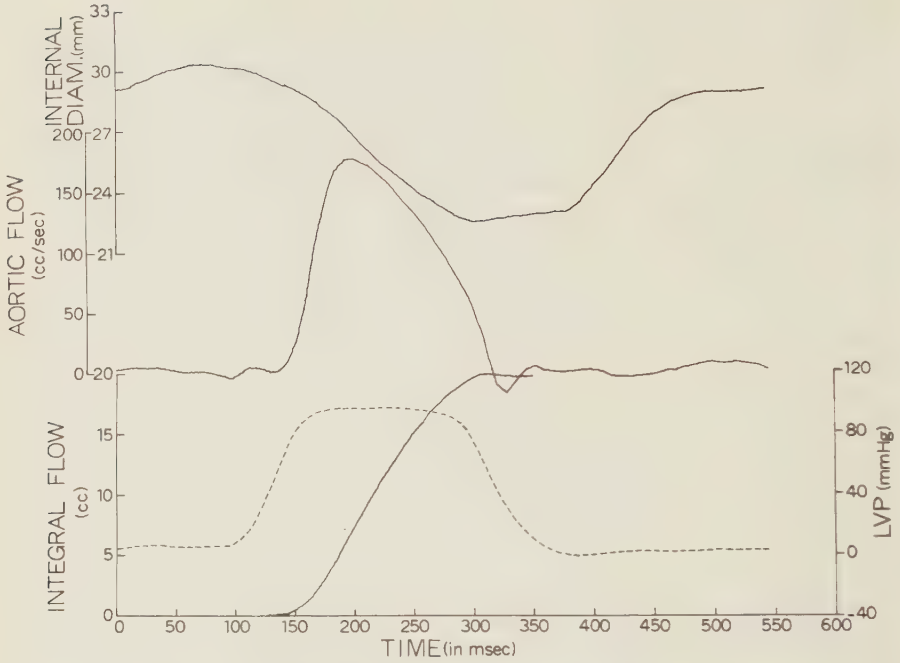

Fig. 4. Computer plot of transverse internal diameter, aortic flow, integral flow and left ventricular pressure. Reproduced, by permission, from *Cardiovascular Research* 6:163, 1972.

pressure and flow by not more than 4-8 msec under the most stressful of experimental conditions. This corresponds with the sampling interval of our digital program. Thus, the diameter may lag the pressure and flow by one sampling interval at most; this would not be significant.

SUMMARY

The techniques described above allow the instantaneous evaluation of the left ventricle in conscious animals in terms of the three basic physical determinants of left ventricular performance: pressure, diameter, and flow.

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39. POSTANESTHETIC AND POSTOPERATIVE CARE

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Care of the surgical patient following implantation may be separated into two general areas: the postanesthetic period and the postoperative period. When surgery is finished, there is the usual feeling of relief that the procedure was successfully accomplished. Cardiovasular instrumentation procedures are generally of long duration which often leads to fatigue of the surgeon and assistants. Therefore, the most likely time for mental letdown is during the postanesthetic period. The intensity of care required will depend upon the degree of surgical insult, the duration of anesthesia, and the preoperative condition of the patient. Hazards of hypotension, dehydration, hypothermia, hypovolemia, acidosis and other conditions will be emphasized in this discussion. Considerations for early and late postoperative care will be presented.

One of the best methods for treatment of postanesthetic complications is good anesthetic management during surgery. Animals are usually fasted 12-24 hours before surgery and water may be withheld as well. Even if the animal is in good physical condition, stores of liver glycogen may be depleted following a 12 hour fast. In some cases, because of feeding schedules and time of surgery, animals may not be fed for 36 hours. Considerable loss of body water can occur from exposed tissues and through the respiratory system during surgery. Intravenous fluid administration at the rate of 10 ml/kg the first hour and 5 ml/kg for each additional hour will prevent excessive water loss. Fluids such as 2½% dextrose in one-half strength Ringer's solution may be used. Dextrose administration is preferred because of fasting procedures before surgery. If blood loss is excessive, fresh whole blood replacement should be used when indicated. Fluid administration should be continued until the animal has recovered consciousness and is able to stand.

Hypovolemia and hypotension may accompany the instrumentation

procedure, which are again best treated by prevention. If blood loss is anticipated, fresh whole blood should be administered during the procedure. If intravenous fluid replacement has not been provided, one can anticipate prolonged recovery and a significant incidence of postanesthetic morbidity and mortality. Hypotension and decreased cardiac output will slow recovery. Elimination of pentobarbital will proceed at a slower rate as tissue perfusion will be decreased. If a high concentration of glucose (50%) is administered during recovery following barbiturate anesthesia, the recovery period may be prolonged (1). However, other fluids may be administered to these animals at the rate of 5 ml/kg/hour without adverse effects.

Most operating rooms are maintained at temperatures of 20-22°C. Evaporation of body fluid from exposed tissue surfaces and ventilation with dry gases make accidental hypothermia a common occurrence (2). When placed on stainless steel surgical tables, cats, primates, dogs, swine and other small animals have a large surface area from which to lose heat. The extent of hypothermia can be observed from data presented in Tables 1 and 2. Only minor surgery was performed on these animals, and I have observed greater and faster decrease in body temperature when the pleural or peritoneal cavity is exposed. In addition, anesthesia increases skin blood flow. When measures are not taken to conserve body temperature during anesthesia, hypothermia will be assured during the postanesthetic period. Preanesthetic use of tranquilizers will prevent shivering and induce a greater drop in body temperature. The consequence is prolonged recovery and possible death. Dale, et al. (3) demonstrated that pentobarbital anesthetized dogs exposed to environmental temperatures below 32°C experienced some degree of hypothermia. The severity and duration were functions of room temperature. At room temperature of 21°C, body temperature will decrease to 32°C or lower and hypothermia will contribute to maintaining anesthesia (4). Metabolic processes are decreased which will delay degradation of drugs such as tranquilizers and barbiturates. If circulating water blankets (Aquamatic K-pad, Gorman-Rupp Industries, Bellville, Ohio) or other measures are not used during surgery, warming procedures must be instituted during recovery. This can be by means of a warm environment, warm intravenous fluids or other heat sources. If electric heating pads are used, severe skin burns may result. Shivering will ultimately occur and oxygen should be provided to meet the increased demand during the rewarming period. Hypothermia shifts the oxyhemoglobin dissociation curve to the left, which makes oxygen less available to tissues upon demand (5). Shivering causes a sharp increase in metabolic rate and oxygen consumption (6). Therefore, an animal may become hypoxic breathing room air which can be prevented by the administration of high oxygen concentration. One must be

TABLE 1

COOLING IN MONGREL DOGS ANESTHETIZED 1 HOUR OR LESS

Weight (lbs.)	Duration (min)	Anesthetic*	Esophageal Temperature °C	°F
15	60	halothane	34	94
15	20	methoxyflurane	35	97
13	40	halothane	37	99
10	55	methoxyflurane	35	97
12	60	methoxyflurane	33	93

* Semiclosed circle system
Oxygen flow, 500 ml/min.

TABLE 2

COOLING IN MONGREL DOGS ANESTHETIZED MORE THAN 2 HOURS

Weight (lbs.)	Duration (min)	Anesthetic*	Esophageal °C	°F
16	170	methoxyflurane	35	95
10	180	halothane	32	90
15	140	methoxyflurane	32	91
13	160	halothane	35	95
10	175	methoxyflurane	33	93
17	200	halothane	35	95
17	160	methoxyflurane	34	94
16	175	methoxyflurane	31	88

*Semiclosed circle system
Oxygen flow, 500 ml/min.

careful not to overshoot the rewarming process and induce hyperthermia. When rectal temperature reaches 36°C, rewarming can be less vigorous or discontinued. Infant incubators can be used for small animals and are useful for routine recovery procedures. Animals less than 20 pounds can be placed in incubators where humidity and temperature can be controlled in a high oxygen environment.

The type of anesthesia one selects for the surgical patient will influence postanesthesia recovery. The use of inhalation anesthetics such as halothane, methoxyflurane, and nitrous oxide will allow animals to recover much faster compared with barbiturates. With good anesthetic management, animals may be in sternal recumbency or be standing within 15 minutes following completion of surgery. Inhalation agents allow more control of anesthesia and metabolic degradation does not regulate recovery. Morbidity and mortality will be significantly less compared with barbiturates, and postanesthesia recovery will be less traumatic for the patient, anesthetist and surgeon.

Assisted or controlled ventilation of the anesthetized patient should be practiced regardless of the choice of anesthetic. Respiratory acidosis can be limited to a certain degree by ventilatory assistance and administration of $NaHCO_3$ will certainly be of therapeutic value. Acidosis increases the nonionized or active form of barbiturates (7). Therefore, if the patient is allowed to become severely acidotic, prolonged anesthesia may occur. In addition, frequent changes in body position should be provided for the prostrate subject. Some form of padding should be provided in the recovery cage or stall to prevent self-inflicted trauma to the recovering patient. It may be necessary for an attendant to hold the animal's head to prevent injury. Application of some or all of these measures will allow the animal, regardless of species, to return from anesthesia with a better chance of recovery from the surgical insult.

Treatment provided in the postoperative period will vary with the type of instrumentation and anatomical location of the surgical procedure. Special attention should be provided to patients recovering from chest surgery. During the thoracic procedure, a chest drainage tube should be placed for removal of trapped air and fluids following thoracotomy closure. This tube should be left in place until one is sure that hemothorax and/or pneumothorax has been alleviated (8). When animals are bandaged around the thorax or abdomen, care must be taken not to restrict thoracic or diaphragmatic movement and cause respiratory distress. If constrictive bandages are required, application should be delayed until the animal has recovered from anesthesia.

During the early postoperative period, daily bandage changes are indi-

cated during the first few days following surgery to keep the surgical incision dry. This does not suggest that all procedures require bandaging. Antibiotics should be administered systemically following recovery from anesthesia (9). The use of antibiotics is recommended to prevent infection during the healing process, especially following thoracic surgery. They are not suggested as a substitute for aseptic surgical procedures. Topical antibiotic application should be made to skin where catheters and cables exit. Antibiotics and dosages for various animal species have been provided (10).

Examination of patients recovering from surgery is an absolute requirement. Animal care personnel should be informed as to the frequency of health checks desired for instrumented animals. Usually, these animals should be observed a minimum of twice a day following a routine physical examination. Blood examination may be indicated and a veterinarian should be consulted to assist in optimum care of animals following cardiovascular instrumentation for chronic study.

It is recommended that an investigator evaluate instrumented animals before instituting intended studies to assure that research subjects meet certain prescribed standards. Normal blood values have been published for small animals (10).

A veterinarian should be consulted if additional information is needed. Comparison of presurgical and postsurgical hematological and physical examination values may be used to establish when an animal has appropriately recovered from surgery and is ready for study. This presumes that presurgical values were within normal limits. One should define animal subjects for research with the same vigor and care as electronic instruments are defined.

SUMMARY

With good anesthetic and postanesthetic care, which includes intravenous fluid administration, heat conservation, and ventilatory assistance, recovery from the instrumentation procedures should be uneventful. Antibiotic therapy, frequent dressing changes and a comfortable environment for postoperative recovery should be provided to the surgical patient to assure ultimate success in obtaining reliable data from the instrumented animal.

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40. DISCUSSION OF SECTION III, IMPLANTATION TECHNIQUES

Panel: Drs. Ernest P. McCutcheon (Chairman), Donald C. Sawyer, and Kitty Fronek

TOPIC 1: Requirements for Animal Health

Before discussion of the various implantation techniques could begin, the general question of what constitutes a healthy animal was asked. This is a very basic question and appears to be a central theme in any research project requiring chronically instrumented animals. The discussion on this subject centered on the dog as the principal research subject, but the considerations raised apply to any animal in a similar situation. How can we distinguish a healthy animal prior to implantation? The most practical and objective method was felt to be the hematological parameters of hematocrit, hemoglobin, and leucocyte and erythrocyte counts. For most commonly used research animals, the accepted normal values and ranges can be found in many veterinary textbooks.

The use of other measures such as chest x-ray, electrocardiography, and blood chemistries would vary with the requirements of the experimental design. Whether single or multiple transducers are implanted, the tests outlined above, and rectal temperature, should be repeated at appropriate intervals to ensure return to the accepted baseline values. Thus in general the standards applied to the chronically maintained animal are the same as those applied to human subjects. For dogs, typical values might be heart rate of 99 beats per minute or below, usually with a sinus arrhythmia; mean blood pressure of 100 mm Hg or below; respiratory rate 28/minute or less, without panting; body temperature 101° F or less, hematocrit 40 to 55%, and body weight stable. The lung fields should be clear, preferably verified by x-ray, and the apparent general health should be satisfactory with alert behavior and adequate, voluntary food and water intake.

No instrumented animal carrying implanted hardware can be considered "normal". With proper criteria, however, it is possible to define the type of chronic animal under study. Every investigator using such preparations should establish, use, and report his standards.

TOPIC 2: Surgical Techniques and Therapy

Other points relevant to management of the surgical procedure and to pre- and post-operative care were emphasized. Premedication for chest implantation will include atropine, xylocaine, and a broad-spectrum antibiotic of choice. (Scrupulously aseptic surgery minimizes the need for antibiotic administration). Heat loss can become a very serious problem if adequate preventive measures are not taken, and some anesthetic agents add to this problem. Any variety of heating pad was felt to be desirable to help maintain the animal's body temperature, but a circulating water blanket is preferable. After chest surgery, aspiration should continue until all air has been removed and chest drainage stops.

Several variations of the implant techniques reported in this section were discussed. Umbilical tape for aortic occlusion, rather than Pott's clamps, was felt to cause less damage to the vessel wall. A spring loaded hemostat with the teeth ground down or with a carbide coating aids insertion of solid-state pressure cells into the heart and blood vessels. The use of plastic sutures, rather than silk, was suggested, since silk is relatively more antigenic. Some type of stabilization of standard flow probes placed around the ascending aorta was felt necessary for successful long-term studies. Stabilization has been accomplished with various materials placed around the aorta or adjacent to the proximal and distal sides of the probe. Dacron graft material, sponge, and curtain materials have been successfully used for this purpose. Narrow probe designs appear to diminish this problem considerably but are not widely available.

Following surgery the antibiotic regimen should be continued for several days. The details of the antibiotic regimen will depend on the criteria used to evaluate the health of the animal. There must be room for clinical judgment, and criteria for antibiotic administration and duration would depend on such factors as body temperature, leucocyte count, overt evidence of infection, and the general demeanor of the animal. The rules cannot be rigid, and duration of treatment is not a criterion per se.

Exteriorized wires should be attended frequently so that they are kept dry. Acetic acid (1%) has been found useful for this purpose, followed by topical application of an antibacterial powder. If an exudate is observed around the wires at the skin exit, culture and identification of the organism will be a useful guide to therapy.

Animals with completely implanted telemetry tend to have a smoother post-operative course than animals with exteriorized leads. If the probe lead is exteriorized, the type of junction is especially important and better ex-

teriorization techniques need to be developed. Various skin plug designs have been tried with rather undependable results. The problems can be decreased by feedback to the manufacturers, to help improve the design of leads, minimize crevices, and improve connectors.

TOPIC 3: Importance of Autopsy

The discussion closed with the reminder that a careful autopsy must be a definite part of the routine. There is an obligation to the animal as well as to the experiment. If the animal died of an acute event such as aortic rupture, the data obtained previously are likely to be valid. If smoldering infection and extensive fibrosis are present, the previous results may be questionable. There are very few, if any, technical assistants who can do this part of the job properly.

SUMMARY

This section described techniques to guide selection, implantation, and recovery of animal subjects. There are many variations of each implantation technique, and usually each surgeon will accomplish the implantation in the manner that is easiest for him. The ideas presented here should be regarded as a starting point for the beginner in both surgery and chronic animal instrumentation. A further bit of advice was offered. Obtaining the goal of a satisfactory chronic animal preparation is usually very discouraging in the beginning. A great deal of difficulty is to be expected, but persistence on a regular and continuing basis will usually result in success.

IV. SIGNAL CONDITIONING AND PROCESSING

Section Editor: Joseph C. Greenfield, Jr.

A. Directly Connected Systems
B. Telemetry Systems
C. Analog Processing
D. Analog-Digital Processing
E. Digital Processing
F. Discussion

41. DIRECTLY COUPLED TECHNIQUES

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The purpose of this paper is to summarize briefly the techniques for measuring various physiologic events through direct or "hard wire" coupling of probes to the recording system. It will serve as a background for evaluating the more elaborate telemetry methods which will be described in subsequent papers.

The majority of studies undertaken to date on chronic animals have employed physiologic probes directly wired through suitable connectors to the amplifier system. The advantage of a directly coupled system is obvious; it is the most reliable method of transmitting a signal from the animal to the recording system. Likewise, the primary disadvantage is obvious; to a certain extent the animal must be restrained. However, investigators have devised many ingenious techniques which allow the animal to carry out most physiologic functions with a minimum of restraint. Thus, excellent studies of exercising animals, i.e., swimming, running etc., have been accomplished. In general, dogs, horses, and perhaps, as we have learned during this Symposium, pigs, do very well using direct coupling techniques. The animal must tolerate the presence of external wire, and in some primates this is apparently a major problem. Telemetry must be used in studies in which the animal must be free-roaming, or in behavorial studies in which any degree of restraint would alter the experiment. However, certainly the majority of physiologic studies can be accomplished with direct-coupled systems and do not require the more complex techniques associated with telemetry.

Blood pressure can be measured with an indwelling catheter placed into the vascular chamber of interest and tunneled subcutaneously to exit on an appropriate spot in the skin (1). The patency of the catheter can be maintained with daily infusions of heparin. At the time of study, a strain gauge is connected to the external end of the catheter and mounted on the animal's back. The connections from a catheter tip strain gauge can be exteriorized

in a similar manner. Blood flow, using either an electromagnetic or ultrasonic flowmeter, can be measured in any of the major arterial or venous vessels. There are various chronic connectors which are commercially available to connect the probe wires to the external cables. In addition to blood pressure and flow measurements, pacing wires, distance sensing devices, and catheters for injection or sampling of blood can also be implanted and coupled in a similar manner.

In our laboratory we have had the best success by bringing the catheters, lead wires, etc. to a subcutaneous pouch on the back of the animal between the shoulders. Two or three days prior to study, after healing has taken place, the pouch is opened and the wires exteriorized. The integrity of the system can be maintained by placing the ends in a suitable harness to prevent the animal from chewing the connectors. By careful asepsis, these couplings can be maintained for a considerable period of time with the animal relatively free of infection.

SUMMARY

In choosing the proper coupling system the investigator should acquaint himself with the available techniques and, where possible, choose the simplest method for making the observations required by his particular study.

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42. BACKPACK TELEMETRY[1]

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The development of transistor and integrated circuit technology and the application of this technology to medical instrumentation has made practical the radio telemetry of basic cardiovascular variables, i.e., flow, pressure and dimensions, from freely ranging, untethered animals. Telemetry of physiological data is desirable for several experimental designs, while it is almost essential for others. We have utilized techniques to radiotelemeter measurements of arterial and ventricular pressures, blood flows, and cardiac dimension in a variety of situations. These techniques have provided the capability for determining the left ventricular and peripheral vascular responses to near maximal exercise in normal dogs (1-4) and those with circulatory impairment (1, 5, 6). In these experiments unrestrained dogs ran spontaneously at speeds of greater than 20 mph for several miles (Fig. 1). Exercise such as this is difficult to obtain with a treadmill in the laboratory environment utilizing "directly coupled" techniques. Another area in which telemetry proves invaluable is in obtaining data from nondocile animals living in their natural habitat (7). The capability for telemetry has enabled description of coronary dynamics in unrestrained baboons (8) and of cerebral hemodynamics in feral giraffes (9). Finally, behavioral physiologists are provided with quantitative measurements of the effects of various spontaneous interactions among animals without the modifying influence of the standard laboratory paraphernalia and environment (Fig. 2).

Thus the usefulness of radiotelemetered data is no longer a question, but the question does arise whether it is advantageous to utilize backpack techniques or to implant the entire system within the animal. There are advantages and disadvantages to both "backpack" and "implantable" techniques. We are currently using the former approach. The goal of this dis-

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Fig. 1. Dog running over 20 mph carrying blood flow and pressure measuring and telemetering apparatus in backpack. The signals are telemetered to a mobile recording unit (not shown).

cussion is to (1) describe the advantages and disadvantages of the backpack technique and (2) describe what is done to minimize its disadvantages.

The most important feature of the "backpack" technique is its relative simplicity and availability for adjustment, repair or replacement. Telemetry transmitters and voltage controlled oscillators are generally sensitive to shifts in battery voltage. Accordingly, it is frequently necessary to check voltage level and it is often necessary to replace defective batteries. The problems involved with maintaining proper battery voltage, even when they can be replaced at will, are magnified several fold when the lifetime battery supply or a system for battery recharging must be implanted at the initial operation. In addition, it is frequently necessary to readjust the telemetry transmitter frequency depending upon where an experiment is being conducted in order to avoid local commercial FM transmission. Thus, changes in transducer characteristics, such as drift in implantable pressure gauges, or changes in proximity to local radio stations, makes the ability to adjust the instruments not only desirable but essential. In other words, the design and fabrication criteria for the measuring and telemetry apparatus are signif-

Fig. 2. Behavioral studies on baboons. One of the animals is instrumented for measurement and telemetry of blood flow and arterial pressure. The instruments are carried in the canvas backpack.

icantly eased when the instruments are exposed for adjustment or replacement.

The second important feature of the "backpack" system is its economy. When the instrumentation is attached outside the animal, one device can be used for telemetering measurements of blood flow and pressure from several animals. This represents considerable reduction in operating expenditure for a laboratory such as ours which generally maintains more than 20 instrumented animals at various stages of recovery and experimentation. Moreover, there is a certain percentage of animals that never reach the stage of experimentation either because of transducer failure or surgical failure. In these cases the additional effort and expense of instrument preparation and implantation would be wasted.

On the other hand, "backpack" techniques have disadvantages as well.

For instance, it is necessary to exteriorize the transducer leads; these are generally brought through the skin in the interscapular area of the back. The wire channels provide a tract for infection to spread from the skin and subcutaneous tissue to the thoracic or abdominal cavities. In healthy animals or even animals with circulatory impairments, e.g., heart failure or severe anemia, this has not been a significant problem. However, it could prove to be a problem in animals whose normal defense mechanisms are altered because of irradiation or massive immunosuppressive therapy, e.g., as in transplantation experiments.

Although systemic infections are infrequent in our experience, localized infections of the wire exits are almost unavoidable. This is especially the case if wires have to be frequently buried subcutaneously and subsequently recovered to protect them from the animals' instinct to scratch or bite. These localized infections are only rarely associated with systemic manifestations of infection, e.g., fever, tachycardia, anorexia and lethargy. The wire exit infections can be minimized if four to six inches of wire are buried in a coil subcutaneously leaving approximately one to two inches protruding from the skin. Within two to four weeks postoperatively the subcutaneious coil is anchored by a fibrous mass. This prevents infection and also serves to prevent either withdrawal of the transducer leads to the thoracic or abdominal cavities or damage to the transducer if the animal reaches the exteriorized portion.

Fig. 3. The backpack used for dogs has been successfully adopted for goats.

Fig. 4. A baboon, carrying the blood flow and pressure telemetry instrumentation in the canvas backpack. The backpack allows almost any type of spontaneous activity.

One method of protecting exteriorized transducer leads is to avoid exterior loops of wire or connectors that can be grasped by the animal. It is advisable to leave only a short length (1 inch) of transducer leads exposed. Local irritation can be limited by minimizing infection and by shaving only a small area where the transducer leads exit. Large shaved surface areas will

often result in irritation and excessive scratching by the animal. Using these precautions, we have found it generally unnecessary to use collars or bandages to prevent dogs from biting or scratching transducer leads. Polyethylene, Tygon, or Teflon catheters or wires coated with medical Silastic will not readily form a fibrous scar subcutaneously. In these cases, or for transducers with connectors, or for animals that cannot be observed daily, the transducer wires or catheters should be buried subcutaneously.

An additional possible difficulty with backpack techniques is that the animal is not completely unrestrained, but can be limited by the backpack itself. However, we have developed lightweight yet durable backpacks which do not prevent dogs from eating, sleeping or from running at speeds of greater than 20 mph (Fig. 1). This same type of backpack can be adapted and is tolerated by larger animals, such as horses or goats (Fig. 3). Another form of backpack has been developed especially for baboons and provides freedom for a variety of spontaneous activities including eating, sleeping, climbing, exercise, or even fighting with other baboons (Fig. 4). An enlarged version of this backpack has also been successfully used on grizzly bears. The main limitation of these backpacks appears to be prevention of assuming the supine position, and after extended use (greater than two weeks), abrasion of the skin in the axillary region may occur. Finally, some animals will simply not tolerate backpacks. Although dogs, baboons and most ruminants will not disturb backpacks, only some chimpanzees will allow a backpack to remain.

SUMMARY

The role of miniature, low power measuring instruments in combination with radio telemetry is well established in the physiological sciences. Still, bio-telemetry is in its infancy. Appropriate instrumentation for measurement and radiotelemetry of only a limited number of variables has been perfected. These instruments suffer from a number of limitations; the primary limitations being stability, accuracy, and power consumption. Significant technical developments are necessary to circumvent these limitations and permit truly long term implantation without intervention. While advances are being made in instruments designed for total implantation, the technical problems are sufficiently difficult that it will probably be some time before such instruments are generally available. For these reasons, we have used "backpack" systems which circumvent a number of the practical difficulties associated with the totally implantable systems. In the "backpack" system, the instruments are available for adjustment and repair, batteries can be changed easily, the size of the instrumentation can be

greater than for totally implanted systems, the system does not require extensive insulation and sealing, and finally, two or three total instrumentation systems can be used for numerous experiments on a large colony of experimental animals.

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43. IMPLANTED TELEMETRY SYSTEMS

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INTRODUCTION

The selection of proper instrumentation to measure various physiological parameters is an important aspect of any experimental research program. Measurements can be accomplished either with a direct wire connection to a recording system or via a radio telemetry link. For acute experiments, the direct wire approach is usually satisfactory, the least costly, and the most easily implemented. But for long term studies which require periodic observations in an awake, unanesthetized, unrestrained state, the use of radio telemetry is essential.

Radio telemetry has been used for biomedical applications in two forms: namely, implanted or external backpack. Backpack systems have often been adopted from developments in other fields since small size compared to the test animal is the principal requirement. But a transmitter that is to be implanted inside the body of an animal has unique requirements that usually preclude use of existing systems. Not only must the physical size be smaller than external systems to avoid impairment of physiological functions, but special moisture protection, long battery life, and extremely low operating power are required for reliable long term data collection. In 1957 Mackay and Jacobsen (1) reported on ingested devices, called endoradiosondes, that transmitted through body tissue. The ready availability of transistors in the late 1950's then stimulated further development of this field (2) leading eventually to units that could be surgically implanted in small animals.

At first, researchers were happy to obtain measurements of such data as ECG and temperature, parameters that could be measured with simple single-transistor circuits. Transistors were still bulky, expensive and not always reliable so that the use of designs with a minimum number of

transistors was essential. Recent developments in transistors and integrated circuits have permitted the design of much more sophisticated circuits to measure a wider variety of parameters with less bulk and higher reliability (3). Another important contribution to the development of biotelemetry has been the adaptation of miniature low power circuits developed for the space program.

Systems attached to the outside of the body can provide a great deal of physiological data on animals, but the types of animals and the circumstances under which they can be used are a frequent limitation. Breakage of leads from the sensor to the transmitter package and damage of the telemetry unit by the animal are typical problems encountered. The most serious difficulty results from the fact that leads coming through the skin invariably cause infection with local complications or retrograde transmission into the chest. These problems can be solved by the use of a totally implanted system. However, new design considerations must be taken into account to insure successful use of the implanted system. This paper describes some of the features that must be considered in an instrument designed for total implantation.

DESIGN REQUIREMENTS

First, and most important, the implant package must be sufficiently small so as not to disturb the normal physiological functioning of the animal. The tolerable size obviously depends upon the size of the animal and the location of the implant package in the body. For instance, a 1-1.5cm^3 temperature or ECG telemetry system weighing 4-5 grams has been successfully used in the peritoneal cavity of 450 gram rats. Larger transmitters, such as multichannel systems weighing 30 grams and with a volume of 25 cm^3, have been used frequently in 15 to 20 Kg dogs. Although technological advances in microelectronics and integrated circuit techniques make it possible to develop very sophisticated electronic systems in extremely small packages, such methods do not solve the power supply problem or the need for micropower operation. Since the implant system must contain not only the electronics, but also the power supply, the use of the smallest possible battery consistent with the required operating life is essential. A most important criterion, then, is the magnitude of the power drain because of its effect on the overall size through the battery requirements.

A power demand from a few microwatts to a few milliwatts has been achieved in the designs to be described. First, all the necessary signal conditioning can be accomplished at the low microwatt level using high gain

transistors and a 1.35-V or 2.70-V power supply. The power requirements of the sensors vary considerably, depending upon the kind of measurements being made. High impedance thermistors require only a fraction of a microwatt for temperature measurements. In measuring biopotentials such as EEG and ECG, the body provides the "sensor" power and only two electrodes are required. In the case of pressure measurements, about ½ milliwatt is required to operate the solid state, strain-gage type cells presently available for biomedical use.

The other major part of an implanted telemetry system is the radio frequency (RF) transmitter. Power requirements here obviously depend upon the needed operating range, antenna efficiency, information rate, and encoding scheme used. To reliably sustain oscillation in the transmitter stage, the 2N918 type transistor used required a minimum current of 0.5 to 0.8 ma or more, using a 1.35-volt mercury cell. This power level will typically provide an operating range of 50 to 150 feet and is more than adequate for most experiments. In order to reduce the average transmitter power demand to the microwatt power level, a pulse modulated RF is used instead of a continuous wave (CW) carrier. This reduces the range to 5 to 10 feet because of susceptibility to spurious noise, but this again is adequate for use with small caged animals, such as rats. Little could be gained in the multichannel system using this technique because of the power drain in the pressure transducers. The alternative used here is to operate the RF stage in a CW mode with frequency modulation (FM) and provide capability for turning the entire system "on" and "of" remotely. This is done with magnetic latching switches or RF-controlled solid state switches which can be activated through the intact skin. Many years of operation are possible from a 500-hour power source, such as a pair of pacemaker cells, if the system is used in a judicious fashion to collect data.

Besides the electrical considerations, proper packaging is critical to assure successful operation because of the unique environment. The body provides almost ideal conditions as far as constant temperature and shock isolation, but the salt water solution in which the system must function is a very hostile environment. Body fluids have an uncanny ability to penetrate almost any plastic encapsulant now available, and obviously, since high impedances are associated with the micropower level circuits used, they are particularly vulnerable to the slightest trace of moisture. The use of glass, metal, or ceramic to provide hermetically sealed cases for all the electronics is the only reliable method for protection of a totally implanted transmitter. Metal with glass-to-metal seals is the most versatile construction technique, but special precautions must be observed to obtain effective RF radiation. Ceramic and glass will not interfere with the RF, but the high

sealing temperatures cause difficulties with the electronics and batteries.

The transmission of RF through body tissue has not proved as difficult as anticipated by some early workers in biotelemetry (2). A frequency of 88-108 Mhz has been used in the designs described, since this range works well and is authorized by the FCC for low-power biomedical use. An exhaustive search for the best transmission frequency has not been conducted by the author, but there are some references in the literature that suggest the frequency is not critical, and therefore, the availability of receivers and the avoidance of special frequency assignments become the principle determinants. In general, the frequency should be high so that a small geometry antenna will radiate effectively, yet at the same time, higher frequencies will be more readily absorbed by the conductive tissue of the body. The higher frequencies can also present a problem since it is progressively more difficult to sustain oscillations in the transmitter stage at low collector currents as the frequency is increased. Taking into account the above considerations, the 100 MHz region is a good compromise.

A SINGLE-CHANNEL ECG TRANSMITTER

Figure 1 shows a single-channel transmitter designed to measure ECG signals. This transmitter is designed to operate from a 1.35V power source and consume only microwatts of power. As pointed out in the previous section on design requirements, electronic systems can be built in extremely small configurations, but the primary limit on size in a totally implanted system is the need for an integral power source. Although a variety of potential power sources, such as atomic power, RF energy beams, body electrodes and mechanical converters, have been suggested and reported in the literature (4,5), the electrochemical battery is, at present, the smallest and most reliable power source available for implant applications.

Aside from the obvious need to cut power consumption to a minimum so that the smallest possible battery can be used, there is another less obvious criterion and that is system operation from a single battery. The reason for this requirement is that much of the space in a small battery is taken up in mechanical packaging, and the volume efficiency diminishes rapidly as the size is reduced. For a required number of microwatts to operate a system, a single cell will provide the power at a considerable reduction in size compared to one using two or more cells.

Although ECG transmitters, using but one transistor, have been reported (6), the circuit of Figure 1 uses six in order to achieve accurate and faithful transmission of the ECG waveform. The number of transistors used in a circuit is no longer a good criterion for circuit selection, since trans-

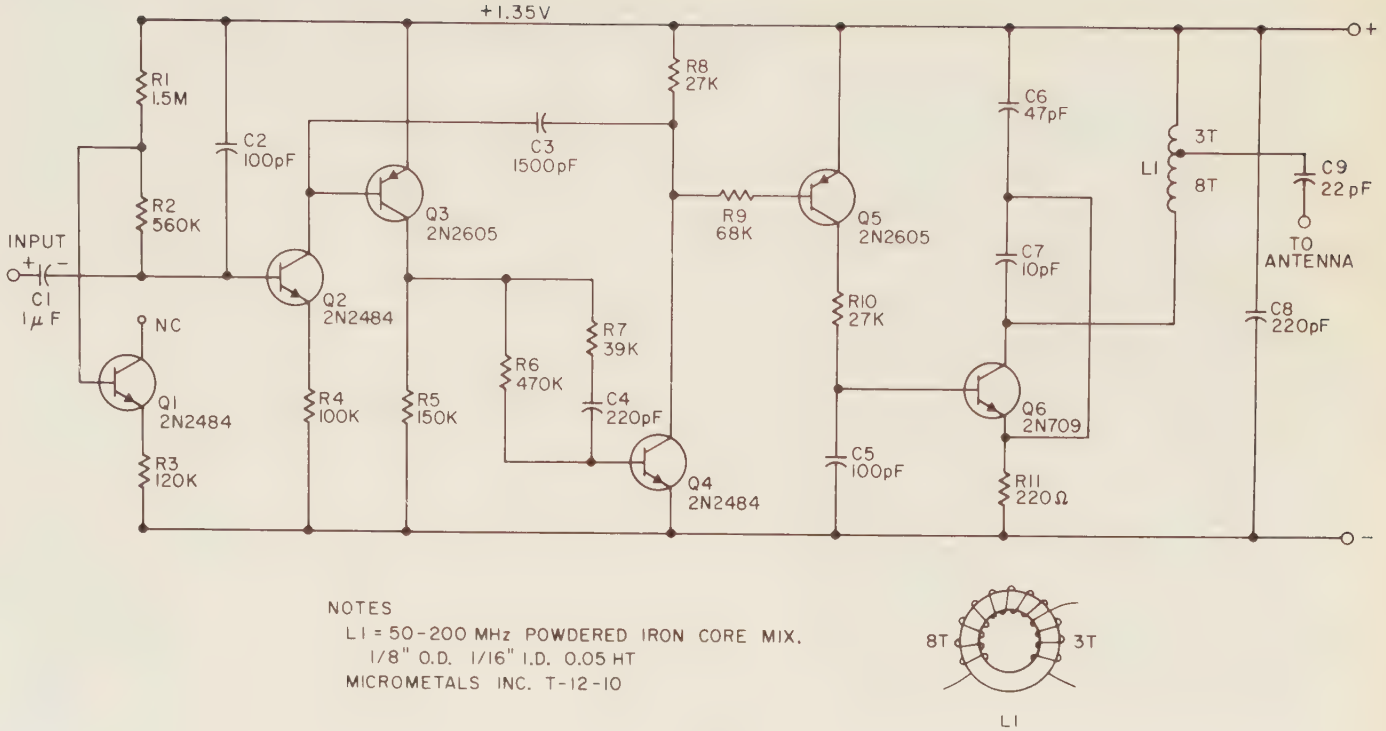

Fig. 1. ECG telemetry system.

istors are microminiature and low in cost. The system size and power consumption are the most important features, along with operational performance.

The transmitter of Figure 1 uses a subcarrier oscillator, Q_3 and Q_4, so that both amplitude and frequency variations in the RF do not affect the accurate transmission of data. Q_3 and Q_4 form a complementary astable multivibrator that will generate short pulses of 25 to 30 μsec duration at a repetition rate of approximately 600/sec for the values shown. An input ECG signal of zero to a few millivolts is coupled to Q_2. This transistor provides a high impedance input and is the current source for the multivibrator Q_3 and Q_4. The input data modulates the current in Q_2, which in turn alters the pulse repetition rate. The ECG data then is encoded as pulse interval modulation (PIM) by this circuit. Q_1 is merely used to bias Q_2, and provide temperature compensation. The pulses from the oscillator cause the RF oscillator, Q_6, to be turned on and off via the switch, Q_5. Data is transmitted by short RF pulses of approximately 30 μsec duration with the interval between the pulses varied in response to the input data. By using a PIM subcarrier, two important objectives are accomplished. First, accurate and faithful data transmission is accomplished irrespective of amplitude or frequency changes in the RF link. Secondly, the power consumption is very low since most of the circuitry is turned off a large percentage of the time.

The system is designed to work at approximately 600 pulses per second with data causing a maximum of ± 5% deviation. Both Q_3 and Q_4, by their complementary nature, are only on during the 30 μsec pulse so that power is only consumed for a short percentage of time, namely: 30 μsec divided by the pulse interval of 1.6 msec or approximately 2% of the time. Q_5 is a switch that turns Q_6 on for the same percentage of time. Therefore, except for Q_2 (which draws about 1 μamp of current) and some bias currents in R_1, R_2, Q_1 and R_3, all of the circuitry is turned off 98% of the time. By this means, it is possible to reduce the average current to 8 μamps. Since all of the circuitry is designed to operate at 1.35 v, only a single mercury cell battery is required. Power consumption then calculates out at only 10.8 μwatts.

Figure 2 is a photograph of a completely packaged system ready for implantation. Even with a more sophisticated circuit design, the size is comparable to many earlier single transistor systems. Due to careful design where the circuitry is off a large percentage of time, the average power is also comparable to more simple designs. The S13E silver oxide hearing aid battery (7.7 mm dia. by 5 mm high, weighing 1 gram) with a 60 mah rating will provide 7500 hours of continuous operation. The slightly larger RM675 mercury cell (11.5 mm dia. by 5 mm high and weighing 2.24 grams) with a rating of 160 mah will provide over 2 years of operation.

Fig. 2. Encapsulated transmitter ready for implantation.

Because of the pulsed type of radio frequency transmission used, the system is susceptible to spurious noises. This normally limits the operating range to 5 to 10 feet. If the RF stage is allowed to operate in a continuous mode and the subcarrier oscillator frequency modulates the RF, considerably greater range of 50 to 100 feet can easily be accomplished, but with a great sacrifice in power consumption (7). Since the RF (when on) draws approximately 0.5 mw, a much larger battery is required or greatly diminished operating life results. The use of remote switches to turn the system on and off can also be used to conserve power.

The circuit of Figure 1 was designed to operate on an absolutely minimum of power when relatively large signals, such as ECG, are to be measured. However, Figure 1 can be used for EEG applications, where only microvolt signals are available, by the addition of a preamplifier. This will also require an extra 10-15 μamps of current (7). Higher input impedances, up to 20 megohms, can also be achieved by the use of a suitable preamplifier.

TRANSMITTER FOR OTHER PARAMETERS

The measurement of physiological parameters other than ECG presents greater difficulties, but can be accomplished by using circuits designed in a manner similar to that already described for ECG. The principle difficulty is in obtaining transducers that do not consume large amounts of power. Signal conditioning (amplification, frequency modulation, pulse coding, etc.) can, with recently available transistors, and with careful design, be

accomplished at the microwatt level. Since the ECG uses only inert electrodes, with energy supplied from the body, no transducer power is required. But for other measurements, such as pressure, considerable power to the transducer is required.

Figure 3 shows the circuit for a pressure telemetry system. A commercially available transducer (Konigsberg Instruments, Inc.) suitable for cardiovascular measurements has been used in our laboratory for the past 5 years. Even with the use of a 5000-ohm strain gage compared to the normally provided 500-ohm one, and the use of a 1.35 v power supply, a current drain of 270 μamps results. This power consumption is 360 microwatts, an order of magnitude greater for the transducer alone than for the entire ECG system. Under these circumstances, a different mode of operation must be employed if long term operation with miniature size is to be achieved. Since only periodic measurements of many variables, such as pressure, are necessary, the use of a magnetic switch or an RF controlled switch (3) to turn the system on only when data is to be recorded will allow extensive operating life even with a small battery. System power drain still must be extremely small by most standards, in the low milliwatts or less, but practical systems can be designed at these levels.

The small strain gage signal from the transducer (approximately 15 mV for 250 mm Hg) is chopped by means of a solid-state switch (Q_1, Q_5, and Q_4, Q_6) and amplified by an AC amplifier, Q_7 and Q_8, with a gain of approximately 5. The subcarrier oscillator, Q_{11} and Q_{12}, operates in the same manner as that of Figure 1, the ECG transmitter, and Q_{10} provides a constant current source that is varied in proportion to the input data. The pulses from the astable multivibrator are applied through C_8 to the binary Q_2 and Q_3 to obtain synchronous operation of the solid-state switches, thereby causing the period of the multivibrator to be controlled alternately by the voltage derived from Q_5 and Q_6. The difference between successive periods is proportional to the bridge unbalance signal, and hence the pressure. An AC coupled amplifier can be used in this circuit to measure static pressure changes because of the chopping technique employed. The pulse interval type of coding makes it possible to transmit the pressure transducer data via telemetry without degrading the accuracy of the signal obtained from the transducer. Obviously, the data can be no better than the transducer, but by using the coding scheme of Figure 3, no additional errors are introduced in the radio telemetry link.

The RF stage, Q_{13}, can be operated either in a continuous mode or pulsed as described for the ECG circuit. The continuous mode will provide ranges up to 100 ft., but will consume about 0.7 mA. Since the transducer alone takes 0.27 mA, the additional current is not an overriding considera-

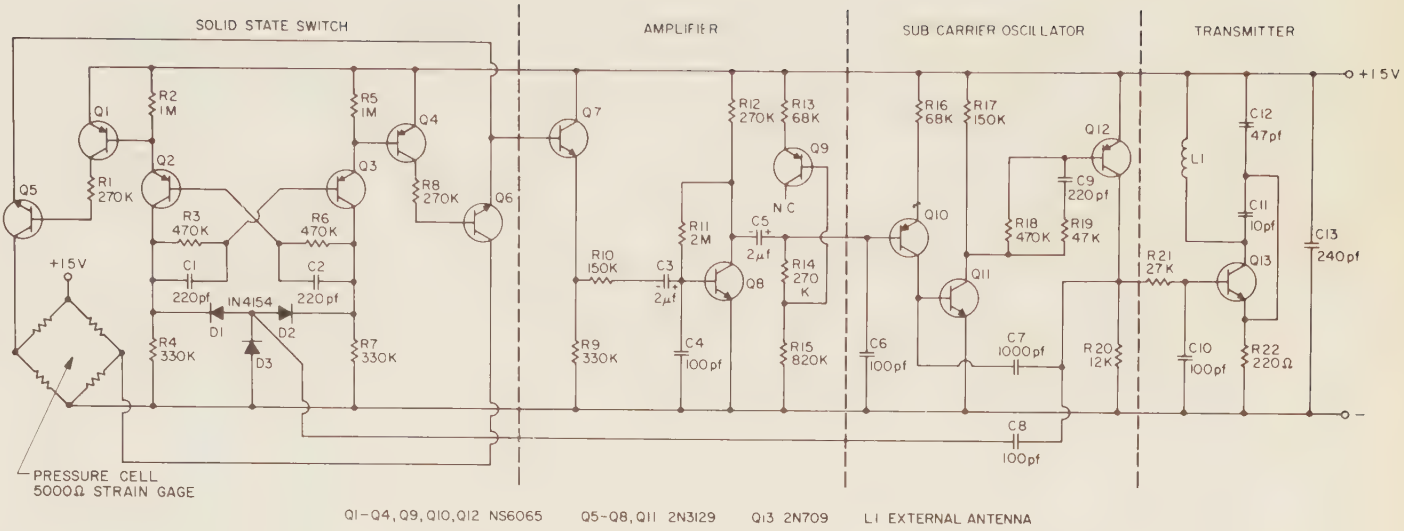

Fig. 3. Pressure telemetry system.

tion for the greater range and reduced susceptibility to noise. Total power is still in the low milliwatts. The use of a 500 mah or 1000 mah pacemaker cell will provide up to a few months of continuous operation. Since it is seldom necessary to take data such as pressure on a continuous basis, the use of a magnetic or RF switch (3) will allow operation up to many years, depending upon the experimental program. Figure 4 shows a typical pressure recording from the left ventricle of a dog's heart.

Figures 1 and 3 illustrate general telemetry techniques to measure two variables, namely ECG and pressure. The two circuits show a wide difference in power drain from microwatts to milliwatts. The controlling factor is the power need of the transducer. The measurement of other variables, such as blood flow, present great problems because of power drain to the transducer. Temperature can be measured with high impedance thermistors that consume very little power and a circuit requiring only microwatts of power similar to the ECG unit is described in Reference 3. The primary problem with temperature is that the normal variation is less than 1°C and great absolute accuracy is required. Accuracy in the telemetry system has been achieved with a circuit similar to the one used for pressure. Besides pressure, any variable that can be sensed with a strain gage transducer could equally well be used with the circuit of Figure 3.

Other than the need to measure a variety of parameters, there is also often a need to record more than one variable at a time. For two variables, the use of two transmitters would be a logical solution. But, when the number of variables exceed three or four, then the use of a multiple system, using only one RF link, is usually desirable. One exception might be if the variables are to be measured in various extremities of the body. Under these circumstances, individual transmitters still might be preferable since the long leads to a control transmitter could cause problems with lead breakage. A single transmitter requires only one receiver and greatly reduces the

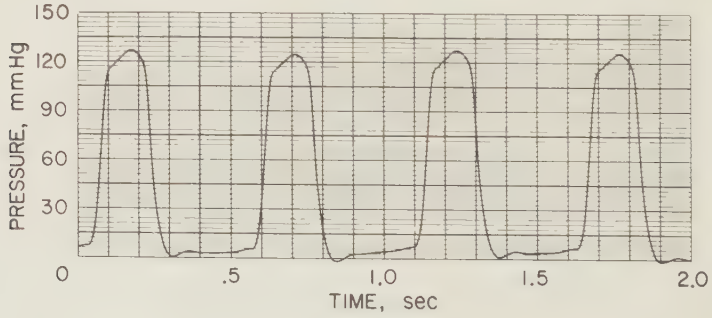

Fig. 4. Left ventricular pressure telemetered from the heart of an active dog.

operational complexity.

For cardiovascular research where many of the variables are to be measured near the heart, the use of a multichannel system is advantageous. A totally implanted system for multiple transducers is described in Reference 3. The system uses pulse interval coding as in Figures 1 and 3, but samples sequentially five to eight different inputs on a time multiplex basis. The signal conditioning and transmitter require only a few milliwatts of power. The system will work with multiple pressure cells and ECG signals. Power consumption of the transducer must be added to the transmitter. Two 1000 mah cells will typically provide 500 hours of continuous operation. Again a transcutaneous magnetic or RF switch is used to turn the system off when data is not being taken.

SUMMARY

Telemetry systems that are both miniature and micropowered and suitable for surgical implantation have been described. Besides the two circuits described in detail, some of the general design requirements for implantable systems have been discussed. Implanted telemetry systems offer many advantages over externally mounted ones with the attendant broken leads and infection problems, but they also pose a circuit design challenge to achieve the small size, low power, and moisture sealing required of an implantable device. Circuits to measure ECG and pressure have been described, but low powered designs for other variables remain to be accomplished.

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44. AN IMPLANTABLE TELEMETRY SYSTEM AND ITS APPLICATION IN THE STUDY OF RENAL HEMODYNAMICS[1]

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INTRODUCTION

The telemetry of blood pressure and flow from untethered animals is a development of the past decade. Thus one of the earliest reports on the telemetry of blood pressure and flow in free ranging animals was made by Van Citters, Watson, Franklin and Elsner in 1965 (1). These early systems combined the use of external electronics to transmit data to remote recording sites with the use of implanted sensors. However, such external electronic packages have several associated problems. The possibility of infection where leads emerge through the skin is high. A degree of control is possible by the use of antibiotics and by aseptic techniques, but protection of the sensor leads and attached equipment is difficult. Ko has pointed out the advantages of totally implanted telemetry. He concludes that future design must aim toward implanting the whole package, thus eliminating problems inherent in external hardware (2).

It is generally agreed that if such implants can be successfully developed for larger animals such as dogs, then a new field for study of the effects of social interaction will have opened up. Studies using mouse colonies only permit episodic blood pressure and electrocardiographic observations while the animal is restrained. By contrast, the use of telemetry in larger animals permits the determination of cardiovascular responses during social interaction and opens up the important area of organ blood flow determination.

After several years of development work, during which external telemetering packages were at first employed in our laboratories in conjunction with implanted sensors, this goal of a totally implantable pressure and flow system has been attained (3, 4, 5). In the initial work on situational stress,

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cardiac rate and arterial pressures were monitored throughout a course of obedience training in the dog (6). At the same time, responses to graded treadmill exercise, natural activity, and incidental situational stress were investigated (7, 8). Later studies involving interaction between a pair of dogs with one dog instrumented provided experience in the design of experiments using situational stress as a provocative stimulus (9, 10). More recently, the development of a totally implantable telemetry system has been accomplished. It provides pressure and flow information on demand and its battery power will permit over 750 ten-minute interrogations in the course of a year (3, 4, 5). It has been used in a preliminary study of behavioral and cardiovascular correlates of individuality in dogs (11, 12, 13, 14).

DESIGN CONSIDERATIONS

A typical channel of information consists of a sensor, a signal conditioner, and a subcarrier oscillator. Common to each channel is a carrier oscillator, a power supply, a regulator, and a power controller. The detailed description of the carrier and subcarrier oscillator is not given in this paper as these units have been described elsewhere (4). Emphasis is on sensors and signal conditioners for detection of flow and pressure.

The two major problems associated with the application of implant telemetry to long term studies are (1) the problem of achieving sufficient operating life, and (2) the problem of achieving long term measurement stability. Micropower must be employed to achieve even a modest operating life. For many cardiovascular measurements, integrated circuits of sufficiently low power consumption are not available, and one must resort to a discrete component approach or become involved in a hybrid development which often produces only a small decrease in volume at considerable cost. The current state of energy sources limits the total operating life to a rather short period if continuous operation is attempted. In many types of experiments sufficient clarity can be obtained by sampling; thus one minute of data each hour might be adequate. This approach prolongs the useful lifetime of the device and trims the data to a manageable quantity. With the expedient of controllable transmission in concert with low power electronics, a package size acceptable for implant and potentially operational for several years can be achieved.

Stability, though often incompatible with low current operation, is of major importance as calibration cannot readily be performed once implant has been achieved. Thus the stability of the slope (sensitivity) and the intercept (baseline) must be held to acceptable limits for years, or some

acceptable technique of calibration must be developed. Achieving long term stability is difficult as sensor and component aging and supply voltage variations contribute to instability. Negative feedback can be employed to control component aging, and voltage regulation can be used to reduce the sensitivity to supply voltage variation. Realization of sensor stability in the required small physical size is perhaps the most difficult problem. The only solution is sound sensor design and application.

BLOOD PRESSURE SIGNAL CONDITIONER

Detection of blood pressure is accomplished by the use of chronically implanted miniature pressure sensors (15). The sensor body is unalloyed titanium 6.5 mm in diameter and 1 mm thick. This material is highly corrosion-resistant, allowing long term direct contact with body fluids. Four semiconductor strain gauges connected in a conventional four-arm bridge are bonded to the inner surface of the small pressure-sensing diaphragm. Positive pressure on the face of the transducer causes resistance changes which are transformed to a voltage change. The sensor is quite sensitive, producing approximately 30 mv/300 mm Hg when used as suggested by the manufacturer. Its frequency response is well in excess of that required to obtain dynamic blood pressure measurements and its temperature characteristics can be determined and dealt with properly.

Figure 1 illustrates a circuit schematic which transforms blood pressure variations to voltage variations and sequentially produces frequency modulation of a subcarrier oscillator proportional to pressure. The circuit consists of a differential input voltage-controlled oscillator with active elements Q_5 and Q_6; a pulse generator consisting of active components Q_1, SCS_1, and Q_4; and a pulse-amplifying circuit consisting of Q_2 and Q_3. The output of the voltage-controlled oscillator turns SCS_1 on, which turns Q_4 on, placing the supply voltage across the pressure sensor. Transistor Q_1 turns on after a delay established by the RC time constant and turns SCS_1 off. The result is an application of a narrow voltage pulse to the pressure sensor on each positive excursion of the voltage-controlled oscillator output. The difference between the pulse levels at the output of the pressure sensor is amplified by Q_2 and Q_3 and filtered by the RC networks connected to the collectors. The resulting DC voltage which is proportional to the pressure applied to the transducer is then employed to modulate the voltage-controlled oscillator. Major advantages of this mode of operation are high sensitivity, low current operation, and the realization of overmodulation protection by the use of a subcarrier with frequency limits.

Frequency limits beyond which the oscillator cannot be modulated are

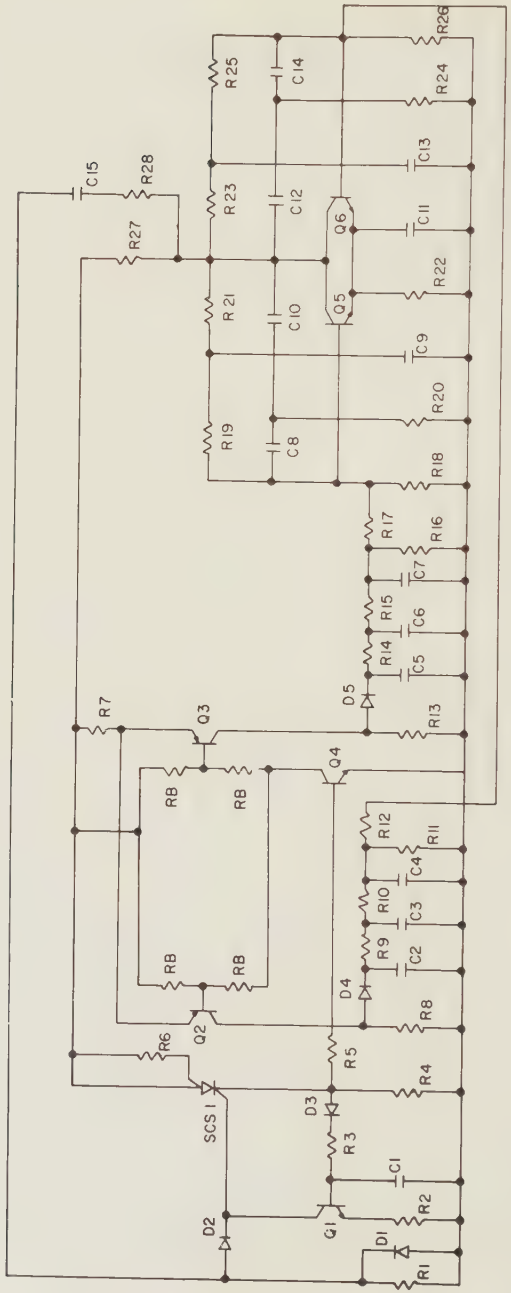

Fig. 1. Schematic of blood pressure circuit. Power is conserved by duty cycling the sensor (RB's) by the action of SCS_1 and Q_4. Reproduced, by permission, from *Clinical Telemetry*, C. A. Caceres, Ed., Academic Press, New York, 1972, in preparation.

realized by operating two parallel-T oscillators with different frequencies of oscillations in parallel with a common collector load. If either transistor is completely cut off, the frequency of oscillation is determined by the circuit connected to the base of the other. When both transistors are conducting equally, the frequency is near the average of the two limit frequencies.

FLOW CONCEPT

Flow detection by an ultrasonic technique was selected because of several advantages. As contrasted with the electromagnetic techniques, the ultrasonic flow sensing probes are lighter, power requirements are less, and the signal level is higher. Several ultrasonic techniques of slightly different modes of operation are available. The back-scatter Doppler is the most popular technique, but suffers from low sensitivity and difficulty of quantifying the frequency shift components with flow (16). The strict time delay techniques require exceptionally accurate time-measuring circuitry as a time differential of a few nanoseconds is produced for a fullscale flow velocity. A phase shift technique reported in 1964 by Plass (17) and refined for extravascular applications in this laboratory was employed, as this technique yields improved sensitivity over either the Doppler or the time delay technique. The block diagram in Figure 2 illustrates the prototype system.

Piezoelectric crystals resonant at 5 MHz are rigidly positioned diagonally across a flow section. The crystals are excited in phase opposition by a continuous 5 MHz signal. The ultrasonic energy from crystal X_1 causes a mechanically-induced voltage to sum with the electrical excitation voltage on crystal X_2. The same is true for crystal X_2 to X_1. These signals are either delayed or advanced in time and are therefore modulated in phase proportional to flow velocity. It can be shown that the ideal output voltage, in terms of the system parameters and assuming a blunt velocity profile, is

$$E = 2\,KV \sin\theta\text{, where } \theta = \frac{2\pi f\, Dv \cot\alpha}{C^2} \qquad (1)$$

and K is a constant, V is peak excitation voltage, f is frequency, D is the vessel diameter, v is the velocity of the blood, and C is the velocity of ultrasonic energy (4). For a small normal value of velocity the phase shift produced is small, allowing the sine of the function to be replaced with the function to give an ideal signal voltage of

$$E = \frac{4\pi\, f\, KV\, Dv \cot\alpha}{C^2} \qquad (2)$$

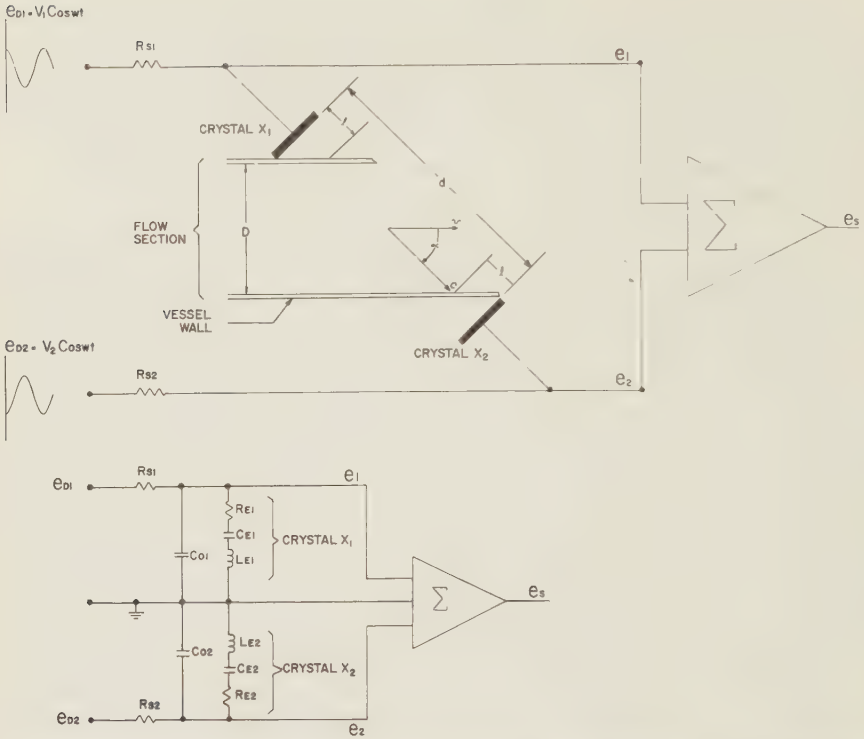

Fig. 2. Flow Concept. The crystals are pulsed in phase opposition for 1 microsecond each 500 microseconds. The phase difference in the incident energy on each crystal yields an output proportional to flow velocity. Reproduced, by permission, from *Clinical Telemetry*, C. A. Caceres, Ed., Academic Press, New York, 1972, in preparation.

For typical probes and probe excitation, the value of KV is approximately 0.5 volt. With f = 5 MHz, C = 1.55 x 10^5 cm per second, and $\alpha = 45°$ the theoretical signal level is:

$$E = 13 \, v \, D \, 10^{-4} \text{ volts/cm}^2/\text{sec} \qquad (3)$$

For flow measurement on a 1 cm diameter vessel with a flow velocity of 100 cm/sec, a 130 mv signal can be realized. This can be contrasted with an electromagnetic level of 0.5 mv for the same position and a pickup signal on the order of several tens of microvolts for the back-scatter ultrasonic technique (7). The selection of the 180° quiescent phase difference between the crystal voltages results in excellent sensitivity.

Critical analysis of the functions used in developing Eq. 2 reveals that many of the parameters are not constant. For example, the velocity C is not constant with either temperature or chemical constituents. The parameter KV is a function of frequency, media properties, and crystal properties. The influence of many of these variables can be reduced by limiting the output from each crystal prior to summation. The limiting is best accomplished by pulsing each crystal for a short period and conditioning the signal received on each crystal before summation. With this expedient, parameter variations which produce errors related only to amplitude variation are significantly reduced. However, parameter variations which produce relative phase shifts between the two received signals still contribute to measurement drifts. These effects are evaluated in subsequent sections.

LOW POWER BLOOD FLOW SIGNAL CONDITIONER CIRCUIT

If the crystal excitations are bursts of sinusoidal voltage defined during the bursts by

$$\begin{aligned} e_1 &= V \cos 2\pi f\, t \\ e_2 &= -V \cos 2\pi f\, t \end{aligned} \tag{4}$$

then the crystal pickup voltages are signal bursts delayed in time by the transit time between crystals and modulated in phase relative to each other by the flow velocity. In ideal form the pickup voltages are

$$\begin{aligned} e_1 &= -K_1\ V \cos 2\pi f\, t + \theta \\ e_2 &= K_1\ V \cos 2\pi f\, t - \theta \end{aligned} \tag{5}$$

where K_1, V, and θ are defined as in the previous case. If the two signals are limited in amplitude and added, and sine θ is replaced by θ, the signal amplitude at the output of the summing amplifier becomes

$$E = \frac{4\pi\, f\, \bar{V}\, v\, D \cot \alpha}{C^2} \tag{6}$$

where $\bar{V}$ is one-half the peak-to-peak limited voltage. As contrasted with the continuous wave technique, for a 1 cm lumen probe and peak-to-peak voltage limit of 1 volt, the pulse technique yields similar sensitivity, but a considerably improved stability. Detection of the signal voltage is slightly altered due to the pulsed nature of the crystal excitation. The real nature of the summed signal amplitude is

$$E = 2\bar{V} \sin \frac{\psi 12 - \psi 21}{2} + \theta \tag{7}$$

where $\psi 12$ and $\psi 21$ refer to phase shifts developed by the combination of the crystals and the excitation and detecting circuitry.

If $\psi 12 = \psi 21 = 0$, the sensitivity becomes $2\bar{V}$ sine θ, and for a small θ this can be simplified to $2\bar{V}\theta$. Figure 3 compares the ideal response curve ($2\bar{V}\theta$) and the response curves determined where $\psi 12 - \psi 21$ has specific values of -.01 and +.01 radians. The maximum electronic error caused by the probe for the drift conditions illustrated is approximately 5% of fullscale.

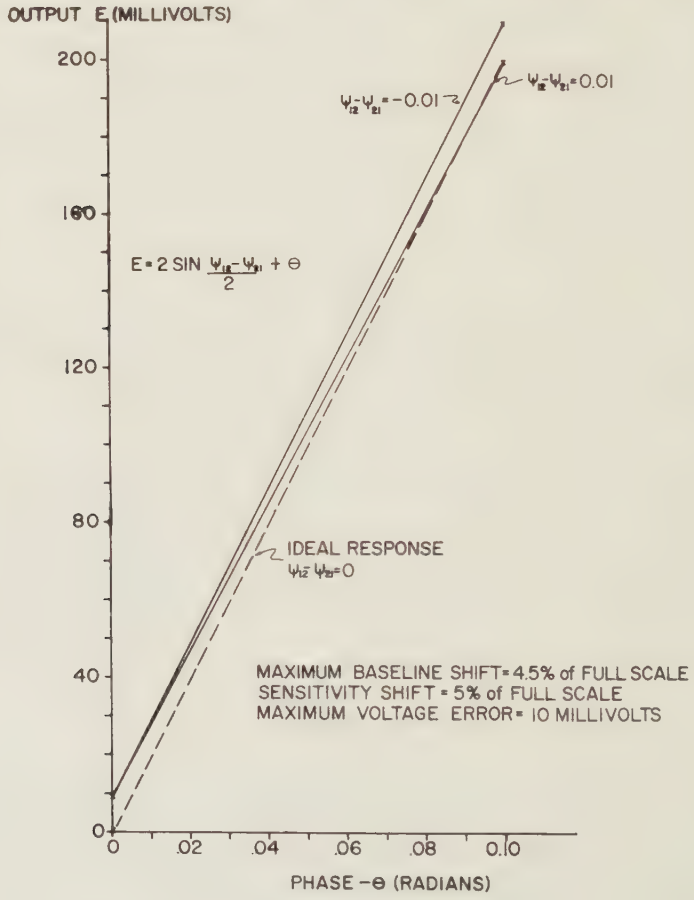

Fig. 3. Flow response curves with various values of residual angles.

Bench testing has revealed that temperature-induced baseline and sensitivity changes will be negligible. Without an in vivo confirmation of baseline, the final basic measurement error is likely in excess of ± 10% of fullscale. The additional error stems mainly from the inaccuracy in measurement of the vessel diameter and the relationship this has to flow quantity. Calibration of the instrument at expected environmental conditions and with a similar vessel on which it will be employed will yield a good calibration. However, this calibration cannot be reliably transferred to final use because of the diameter uncertainty in actual use. However once the probe is grown in place, the precision is likely quite good. There is an error in the absolute value, but this error is reasonably invariable. If the baseline can be established after implant by in vivo techniques (i. e., brief cardiac arrest), then the accuracy can be somewhat improved.

The circuit required to perform the described operation is shown in Figure 4. Each positive peak of the subcarrier oscillator turns on SCS_1 and forward biases the 5 mHz oscillator transistor and the 5 mHz crystal driver amplifier transistors Q_1 and Q_2. When Q_5 is sufficiently forward biased, SCS_1 turns off. The voltage pulse generated by SCS_1 is limited by the series diode stack D_2 - D_5 through R_{11} and deposited on C_7 which in turn charges C_9 through R_{13} and R_{14}, turning on SCS_2. The delayed pulse generated by SCS_2 is then used to gate both the limiting amplifiers and the output amplifier just prior to the arrival of the incident acoustical energy at each crystal.

The on-time of the amplifiers is controlled by the time constant determined by R_{19} and C_A. The component network connected to the emitter of Q_{13} rectifies and filters the amplified RF signal, producing a DC signal proportional to flow velocity. The output is then connected to a subcarrier oscillator to produce frequency modulation proportional to flow velocity.

REGULATOR AND POWER CONTROL CIRCUITRY

In order to realize reliable implantable devices which will operate for several months, it becomes necessary to limit the transmission time to a small percentage of the intended implant life. A radio frequency actuated switch which enables transmission to be controlled by the investigator is one solution. Transmitted energy is received and detected by an inductance-capacitance-tuned circuit in the base circuit of a high gain amplifier. The amplifier turns on a silicone control switch which can be set for the desired on-time. This mode of operation allows command of transmission and insures against battery decay due to accidental turn on by extraneous sources.

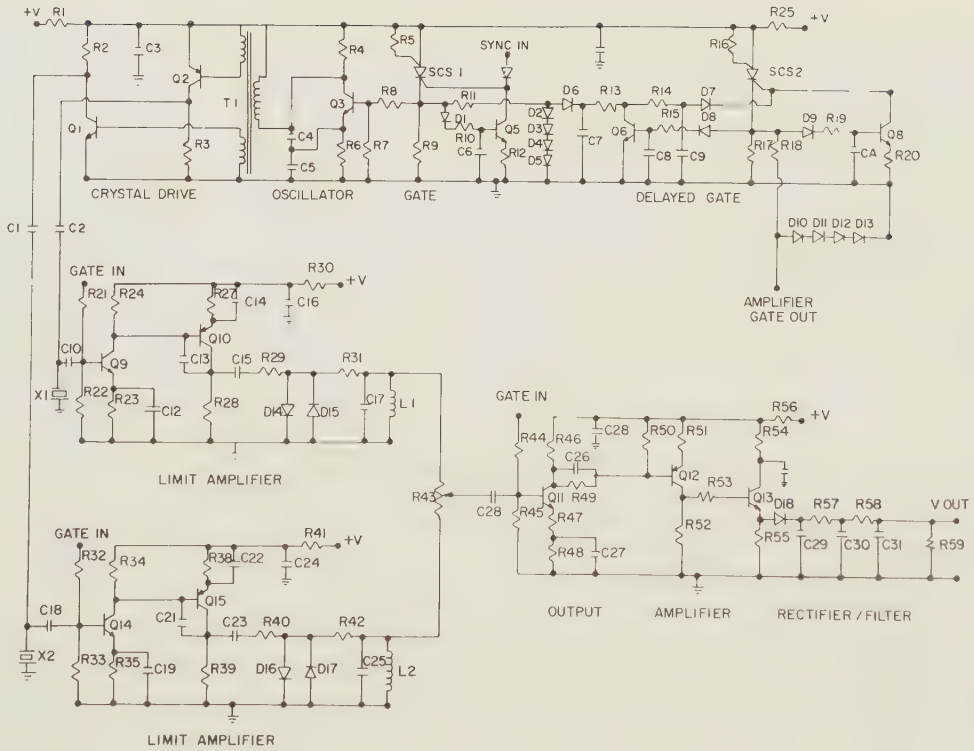

Fig. 4. Flow Circuit. The crystal drive and the amplifier gating are arranged so that only the primary incident energy term is seen on the amplifiers. Reproduced, by permission, from *Clinical Telemetry*, C. A. Caceres, Ed., Academic Press, New York, 1972, in preparation.

At the top of Figure 5 is the circuit developed for the control function. Transistors Q_1 and Q_2 comprise a high gain amplifier which amplifies the signal induced across the tank circuit. This signal is rectified and employed to turn on SCS_1 and initiate transmission. Capacitor C_4 then charges, and through Q_3 the charge turns on SCS_2, which through its influence on Q_4, turns the entire system off and terminates transmission. The regulator in the control circuit is shown in detail at the bottom of Figure 5.

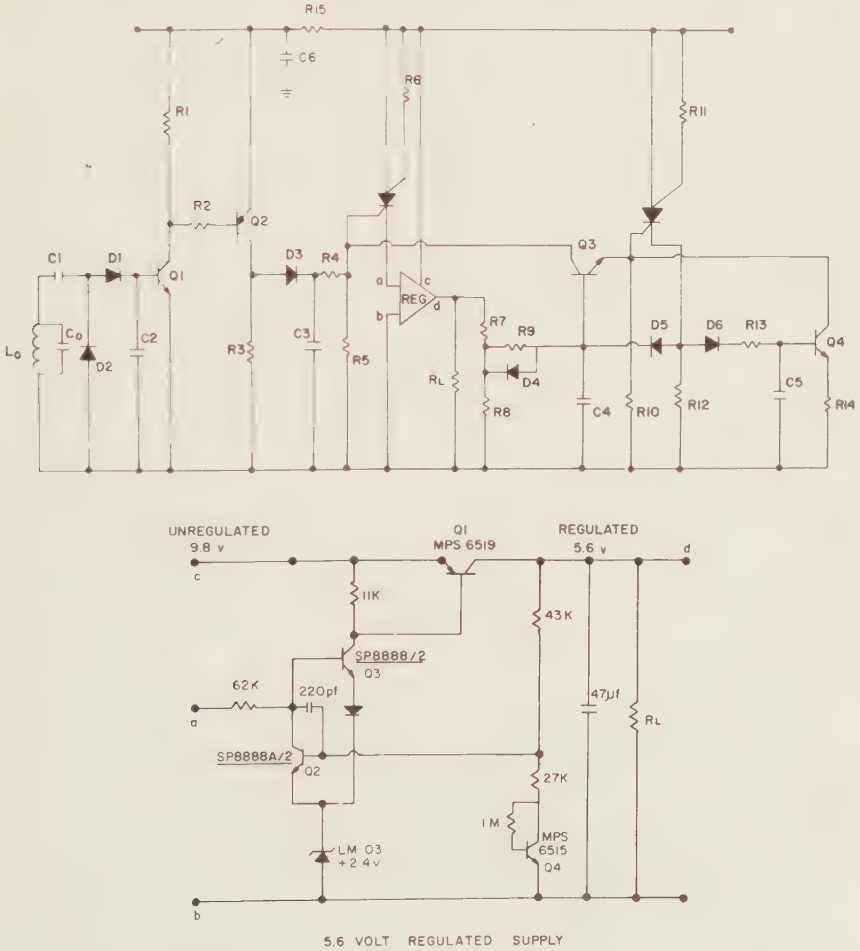

Fig. 5. Circuit schematic for the radio frequency activated switch and for the voltage regulator. Reproduced, by permission, from *Clinical Telemetry*, C. A. Caceres, Ed., Academic Press, New York, 1972, in preparation.

APPLICATIONS

Figure 6 illustrates the package with pressure sensor and flow probe attached. Each amplifier, voltage regulator, power controller, and oscillator is assembled and potted, then interconnected within the package. The package was fabricated from cast acrylic and the cover is attached by screws and sealed with an O-ring. The pressure sensor and flow probe are attached to the package by removable miniature connectors. Prior to implant and at termination of final testing, the remaining space within the package is filled with beeswax for added protection against leakage. Used with a 160 ma hour battery, the unit pictured will operate continually for approximately 100 hours. The controller is typically set at 8 minutes giving a potential of over 750 actuations. At an average of two recording events per day, an operating life of slightly over one year is available.

The ultrasonic flow probe is a thick-walled acrylic tube with crystal faces placed at 30 degrees to the direction of flow. A slit in the tube allows the vessel to be placed between the crystals. The slit is closed by a press-fit slug. The leads from both crystals emerge from the tube tangent to the circumference and opposite to the gate. Calibration of the flow is accomplished prior to implant by placing the probe in a fixture and forcing known quantities of fluid through in varying times. Sensitivity is typically 0.1 volt output per ml/sec. Conclusive flow calibration can be achieved only by an actual calibration of the probe on the vessel to which it is attached. On the renal artery this can be accomplished in two ways: first, by comparing the mean artery flow as determined by the implanted probe and electronics with a collection of the flow from the renal vein during the same period; and second, forcing fixed amounts of blood through the excised vessel in a known time and comparing the voltage readings to the measured flow. The second technique allows a calibration which is acceptable if air can be

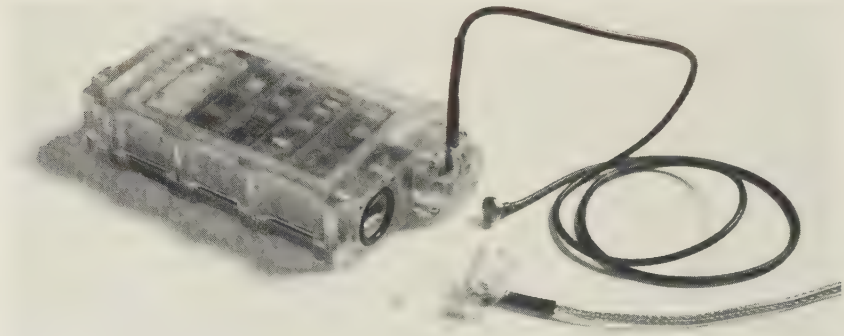

Fig. 6. Two channel flow and pressure transmitter.

excluded from the blood being forced through the vessel. A combination of preimplant calibration and proper scaling for vessel diameter, and confirmation by either one or both of the in vivo techniques yields a calibration factor which, although perhaps not absolute, is sufficiently accurate for many experiments.

Pressure calibration is conducted prior to implant by standard manometric techniques, and pressure recalibration is conducted periodically after implant by comparing the transmitted pressure to pressure obtained by cannulation.

The implant technique is straightforward. The flow probe is placed about the renal vessel and a small gate inserted to retain the vessel within the probe. The pressure sensor is inserted through a small incision in the abdominal aorta and sutured in place. The package is sutured against the abdominal wall. Pressure signals are of high quality immediately postimplant; however, several days are required for reception of a quality flow signal, as a finite length of time is required for the flow probe to grow in. To date an implant time of four months has been achieved.

Recordings obtained during an exercise episode are shown in Figure 7. Exercise was preceded and followed by 3 minutes of stand-stay on the treadmill. Exercise consisted of running on a 15-degree incline for 3 minutes each at 2 and 3 miles per hour, and for 5 minutes at 4.5 miles per hour; then back to 2 miles per hour for 3 minutes. For this dog, mean pressure fell at the onset of exercise, with perhaps a slight increase in mean blood flow. Pulse pressure fell while pulse flow increased. Throughout the course of the exercise, mean pressure increased and mean flow decreased, while pulse pressure remained substantially unchanged and pulse flow increased. Since mean flow decreased and mean pressure increased, the absolute value of the resistance to flow increased. Also at the onset of exercise, the rate of flow change (df/dt) increased, and the rate of pressure change (dp/dt) remained constant; while throughout exercise, both df/dt and dp/dt increased. At cessation of exercise, mean blood pressure increased, and the pulse flow returned to substantially the same level existing at preexercise. These results indicate a decrease in resistance to renal blood flow at the beginning of exercise, followed by an increase in resistance as exercise continues. These observations tend to support cortical-to-medullary flow shifts.

Evidence for the cortical-to-medullary flow shift can be gathered by considering the characteristics of the flow throughout the exercise episode. For a rough approximation, flow to the kidney (18) can be defined by

$$f = C\frac{dp}{dt} + \frac{p}{R} \tag{8}$$

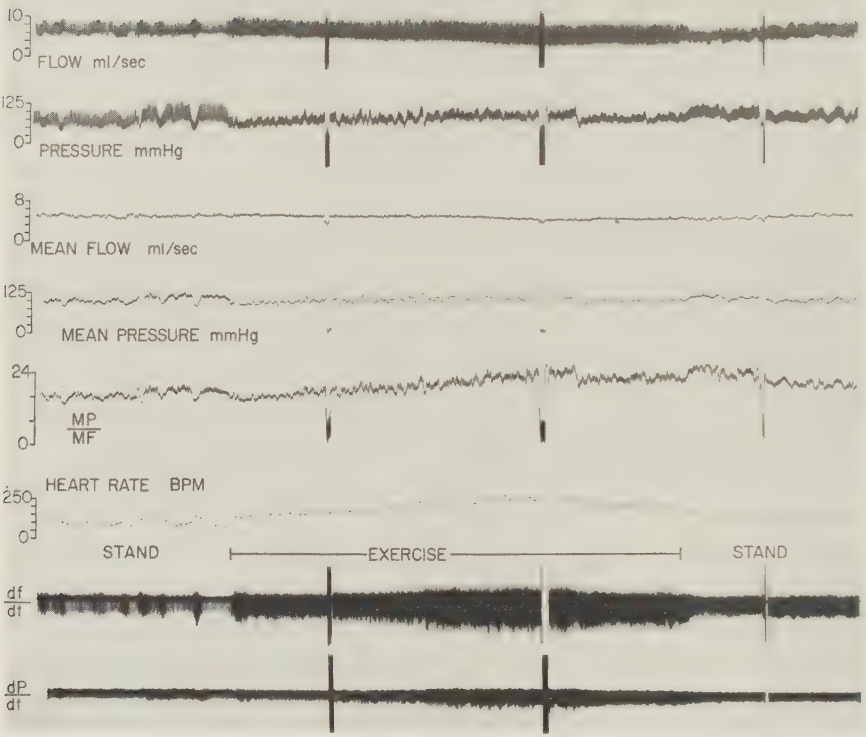

Fig. 7. Data obtained from an exercise event. An instrumented dog was exercised on a treadmill inclined at 15 degrees sequentially at speeds of 2, 3, 4.5, and 2 mph for respective periods of 3, 3, 5, and 3 minutes. Three-minute control periods preceded and followed exercise. From taped dynamic pressure and flow, mean pressure and flow were electronically calculated and the absolute resistance to flow determined by electronically dividing mean pressure by mean flow. The time rate of pressure and flow change was electronically generated to aid in analysis of the hydraulic impedance. One apparent conclusion is that at the start of exercise, mean renal flow remained constant as a consequence of vasodilatation, but throughout exercise, decreased because of vasoconstriction. The increase in df/dt postexercise relative to preexercise indicates an increasing system compliance.

where f is flow in ml/sec; p is pressure in dynes/cm^2; C is compliance, defined by $2\pi r^3/E\ell t$* where r is the vessel radius, t is the vessel wall thickness, ℓ is the segment length, and E is the modulus of elasticity; R is resistance, defined by $8\eta\ell/\pi r^4$ where η is the blood viscosity. The factor df/dt is thus defined by

$$\frac{df}{dt} = \frac{Cd^2p}{dt^2} + \frac{1dp}{Rdt} \tag{9}$$

On the basis of Eq. 8, at the onset of exercise, since initially there was no change in peak dp/dt, yet there was an increase in maximum flow and a decrease in minimum flow, it would appear that C increased and R remained unchanged, or R decreased and C remained unchanged, or both C increased and R decreased. Comparison of a term labeled systolic resistance, determined during systole, where dp/dt is zero, confirms that the resistance has decreased (i.e., radius increased) from its preexercise value. Since C is directly proportional to the third power of the radius r, it can probably be concluded that the compliance has increased.

As exercise continues, the mean resistance increases, which implies decreasing radius and therefore a decreasing compliance; yet, the pulse flow remains high or increases relative to preexercise values. These observations must be considered in light of the fact that dp/dt also increases during this period. Equations 8 and 9 indicate that the character of the flow is influenced to a substantial degree by dp/dt. Thus the direction of compliance from shortly postexercise to near completion of exercise cannot be reliably deduced without an extensive analysis of magnitudes.

Postexercise, the mean flow is definitely reduced relative to the start of exercise in the face of a relatively elevated pressure level. Pulse flow has decreased to slightly above preexercise levels and slightly below onset of exercise levels. The resistance value as judged by the minimum flow level has certainly increased from preexercise, allowing a conclusion that the effective radius has decreased. The time rate of pressure change has returned to its preexercise value, but the compliant component of flow determined at onset of systole is as large or larger than preexercise values and one tends to conclude that the compliance has increased or remained unchanged over preexercise levels. A decrease in effective flow area through the kidney without a concomitant decrease in compliance appears inconsistent with traditional concepts of hemodynamic impedances because within a distensible flow channel, as the radius decreases so does the compliance. This

*A more precise formula may be $\frac{2\pi r^3 \ell}{Et}$

phenomenon of a decreasing radius and an increasing compliance could occur if flow shifted from many cortical vessels to fewer larger-diameter, more compliant vessels in the medullary area of the kidney.

It is conceded that the arguments presented in support of theories suggesting a shift from cortical to medullary flow are circumstantial. Direct evidence is necessary to support these contentions. However, this argument has been presented to lend credence to the application of telemetry and to furnish justification for removing it from a developmental stage to one of useful application. Because of the role the kidney may play in essential hypertension, it can be convincingly argued that the research application of telemetry of the type just described is valuable. If additional evidence can be obtained to support the impedance concepts presented above, then one has a valuable indirect measurement of renal responses which could be applied to research in renal hypertension.

SUMMARY

This paper summarizes a program undertaken to develop an implantable telemetry system for application to chronic cardiovascular research. The design goals for the implanted system are presented and concepts of pressure and flow measurement are discussed. Because of the role the kidney may play in essential hypertension, emphasis is placed on the applicability of telemetry in the study of renal hemodynamics. Consequently, the relationship between pressure, flow, and hydraulic impedance is discussed. Results of an exercise study are given.

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45. INTRODUCTION TO ANALOG PROCESSING OF PHYSIOLOGICAL DATA

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The goal of data processing should be to transform the data into a form which describes the results of the study or experiment, has adequate accuracy and reliability (this is essential), yet is low in cost and is convenient to obtain (this is secondary, but important). There are three general approaches to such data reduction: manual, digital, and analog.

1. *Manual Processing.* The old stand-by is the manual reduction of raw data by the investigator or his technician. The problem is the great expense involved due to the cost of labor, on the one hand, and the tedium and proneness to mistakes, on the other. When done by the investigator, informed choices of data to be used for detailed study and an understanding of the nature and quality of the data become more obvious than when using automatic techniques.

2. *Digital Processing.* At the other extreme, the raw data are accurately converted to digital form and processed with a digital computer. The problem here is that, although the precision may approach the ultimate, one is dependent upon an expensive, complex system, such as a dedicated computer or telephone hook-ups to time-sharing equipment. Although the cost per unit rapidly decreases with increased volume using the digital computer, the expense is high if high frequency components of data are needed. Thus, if only a few data points are collected per second, time-sharing of computer facilities over telephone lines is most feasible and relatively inexpensive. If many channels of data, requiring sampling rates of 100 or 1000 per second are required, the connection to a remote digital computer may become exorbitant or the amount of disc storage with the dedicated computer unreasonable. For large volumes of routine data, there is little real alternative to digital computation. In the future, the cost benefit ratio for digital computing will likely place on-line digital processing at a reasonable level and so will be widely used. Until the time comes that such costs are re-

duced, the technology strengthened, and the availability ubiquitous, a third alternative must be further considered and exploited: analog processing.

3. *Analog Processing.* Although there is no question as to the need for digital processing for many problems, analog processing, particularly pre-processing, may provide improved cost-benefit ratios, plus increased reliability.

Analog pre-processing is usually present in the form of amplifiers taking the signal from the transducers to reasonable levels for analog-to-digital conversion. Furthermore, it is not unusual to have some noise reduction by limiting the band of frequencies passed by these amplifiers. Further processing is relatively easy.

APPROACHES TO PROVIDING ANALOG EQUIPMENT

There are several approaches in implementing analog processing.

One may start from scratch with discrete components. This is for either the rank amateur or the professional manufacturing-design engineer.

Another approach is to use the readily available operational amplifiers for black-box construction for specific operations, e.g., multiplication, filtering, derivatives. Of utmost importance is use of quality components. Operational amplifiers costing $2 and less are available, but let the industrial engineers make proper use of them. The $50-200 variety have high gain, high input impedance in both common and differential mode, low voltage and current offset, low drift, high output current, reasonable tolerance to short circuits at the output and over-voltage at the input, high frequency response, and good stability. It's almost all in the package.

A third approach is use of the ready-made small analog computers, such as the Electronic Associates, Inc., Model TR20 (Princeton, N. J.) The ready-built computer is to be preferred because it has amplifiers of high gain and excellent stability, a built-in power supply, switches for monitoring amplifier output, overload indicators, integrator mode-control, and can easily be repatched for different problems, as well as being used as part of servo-loops for control systems for the research experiments.

Advantages of analog processing, in general, include:

1. A relatively simple and reliable system is available, especially if an analog computer is used.

2. High speed handling of data is easily accomplished, e.g., 1000 Hz or better. This is equaled only by approximately 10,000 samples per second of A/D conversion for digital processing.

3. It is under user control, in contrast to time-sharing on a digital computer, with the problems of reliable communications and computer down-time.

4. The accuracy of computation is as good or better than the data available. Thus, added expense or time for more accurate computation is difficult to justify.

The field is too large to cover even a fraction of the subject of analog processing. Adding, subtracting, multiplying and dividing are rather straightforward, if proper equipment is at hand. Philbrick-Nexus has a most useful handbook for the construction of black-box units, including active filters (1). Burr-Brown has one on general equipment (2) and another for active filters (3). Korn and Korn's *Electronic Analog and Hybrid Computers* (4) is also useful. Carlson et al (5) provide an excellent handbook for use of analog computers.

We have described computation of mean transit time (6), servo-control of pressure and flow (6) and control of a pneumatic cuff (7).

SUMMARY

Data processing using analog techniques offers advantages of simplicity, reliability, effective high-speed data handling, user control, sufficient accuracy, and a high cost-benefit ratio. Representative applications will be described in the following two papers, using computation of derivatives and of cardiac output as examples of the mathematics and approach. Both applications can be adapted to digital processing; the precautions to be observed are similar.

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46. COMPUTATION OF DERIVATIVES[1]

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INDICES OF CARDIAC PERFORMANCE

Why compute derivatives? For the investigator of cardiac function, they give a measure of "contractility". The mechanical and biochemical correlates of cardiac contraction were recently reviewed by Katz and Brady (1). Three parameters of cardiac performance are available: (I) The *rate* of actin-myosin interaction and so energy transformation seems to be measured by the maximal contractile element shortening velocity (V_{max}). This parameter, considered by Sonnenblick, Braunwald, Covell, Ross, and Urschell (2, 3, 4) to be synonymous with contractility, is difficult to measure, since the heart-muscle force-velocity characteristics are significantly different from those of skeletal muscle, and extrapolation to obtain contraction velocity at *zero* load (force) is both complicated and based on numerous tenuous assumptions. (II) The *number* of active interactions between actin and myosin is measured by the maximal isometric tension (P_O). This parameter may be measured by occluding the aorta during systole to obtain the peak systolic isovolumetric pressure – a technique not readily accomplished in the chronic animal and one with some danger to the subject even if it lasts for only one beat. (III) The *rate of activation* of the actin-myosin interactions is measured by the rate of tension rise (dP/dt) when effects of internal elasticities are eliminated or corrections made. Although related to V_{max}, dP/dt is related to the rate at which actin interacts with myosin, while V_{max} indicates the rate of energy transformation once the interactions are made (1).

It should be clear that the theoretical relationships are not as yet well enough established to provide unequivocal bases for measurement of myocardial characteristics. Nonetheless, it seems certain that the rates of change in pressure or volume of the ventricle will be part of the eventual techniques. Frank, Starling and Wiggers all found such rates to increase

[1] These studies were supported, in part, by Public Health Service grants HE07723 and H6308.

under conditions of increased vigor of contraction, and more recent investigators have supported this concept.

The maximum rate of change of ventricular pressure, dP/dt_{max}, which occurs during the isovolumetric phase or the early part of the ejection phase, is thus a useful index (2, 5, 6). However, this rate is changed by changes in end-diastolic fiber length or load. A still better empirical index of the state of contractility of the ventricle is the maximum value of the ratio between dP/dt and the instantaneous ventricular pressure, P. This index $[(dP/dt)/P]_{max}$ is related to contractility as measured by ventricular function curves and is relatively independent of changes of pre-systolic fiber length (Starling relationship) (7,8). Dividing the ratio by a constant and extrapolating to zero load gives the V_{max} of Sonnenblick, et al (2).

The derivative can be computed and then divided on-line by the instantaneous pressure using analog equipment. It is easier, computationally, to use the mathematical relationship:

$$\frac{dP/dt}{P} = \frac{d(\ln P)}{dt} \tag{1}$$

Recall that:

$$d(\ln x) = \frac{dx}{x} \tag{2}$$

and that one can divide both sides of the equation by dt, giving:

$$\frac{d(\ln x)}{dt} = \frac{dx/dt}{x} \tag{3}$$

Thus, to obtain an estimate of cardiac contractility, accurately measure the dynamic ventricular pressure, take the natural log (or 2.303 times the log to the base 10), compute its derivative and note the peak value. Analog equipment is readily available, although pitfalls are present, as will be discussed. [Computing an index based on developed pressure is still better, according to Grossman et al in 1972 (15).]

COMPUTATION OF DERIVATIVES

To obtain the derivative of a signal, the simplest approach is to use a capacitor, C, some place between the source, E_i, and the readout device, E_o. An appropriate load resistor, R, is added. Values of R and C are chosen to give a time constant (in seconds) equivalent to R (in megohms) times C (in microfarads) which is small enough to obtain the desired derivative over the range of frequencies of interest. In general, the input-output relationship is simple:

$$E_o/E_i = \omega\tau \tag{1}$$

Here, ω is the frequency of the component of data in question in radians per second, and τ is the time constant in seconds or its equivalent, ohm-farads. With a constant input amplitude and time constant, the output of this system should increase proportionately with frequency, a 10x increase per decade increase in frequency, as predicted by the equation. The response should also be 90° out-of-phase, as would be expected from a differentiator, since:

$$d(\sin \omega t) = \cos \omega t \, d(\omega t) = \omega \cos \omega t \tag{2}$$

Here, t is time and ω is a constant, the frequency in radians per second; the cosine being 90° out of phase with the sine. Fortunately, or unfortunately, such a passive system has no gain, and so the response asymptotes with:

$$E_o/E_i = 1 \tag{3}$$

At the characteristic frequency, f_c, the response is down 3 dB ($\sim$30%) and the phase error is 45°. This characteristic frequency in radians per second, ω_c, is the reciprocal of the time constant in seconds.

Some deviation from the ideal occurs at $\omega_c/10$. To make a usable system, then, choices must be made.

a. Decide on the highest frequency of interest in the data, e.g., 16 Hz or 100 radians per second (since $\omega = 2\pi f$) for most cardiovascular studies.

b. Multiply this by 10, and call it, ω_c (e.g., 1000 radians/sec). The factor of 10 is used because the response has only a 0.5% amplitude and 6° phase error at 1/10 of ω_c.

c. Take the reciprocal of ω_c (0.001 in the example) for the time constant, τ;

d. Pick a reasonable value for R, e.g., 0.01 megohm, and then use the calculated value for C (0.1 μfd) for the capacitor, using the equation,

$$\tau = RC \tag{4}$$

This system works, but . . . there is no gain and, if the differentiation is followed by more amplification, rather large amounts of high frequency noise may be present.

A solution is use of an operational amplifier for gain as well as for more adequate high frequency attenuation (9, 10). In the upper lefthand corner of Figure 1, the open-loop, high gain, polarity inverting, operational amplifi-

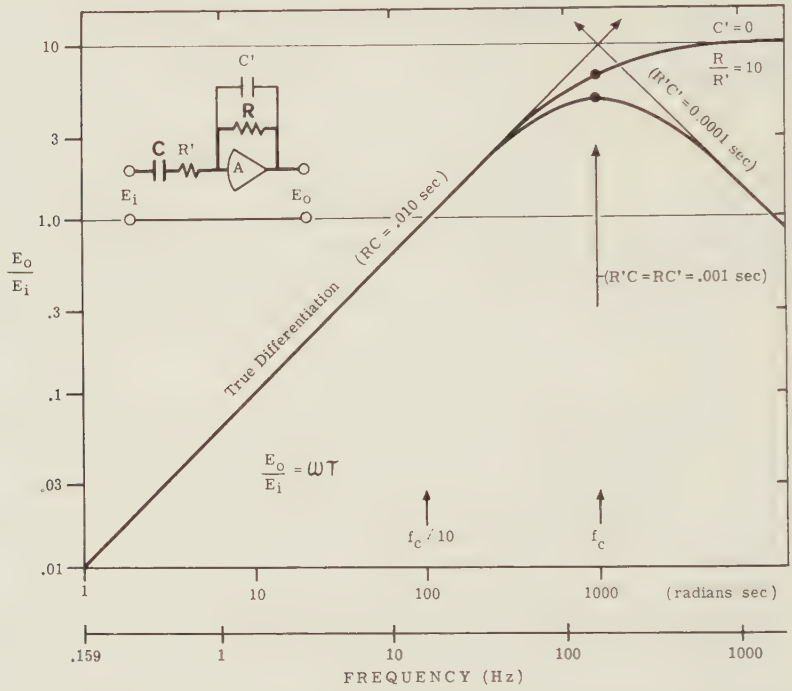

Fig. 1. Analog computation of derivatives; R = 0.1 M, C = 0.1 μfd, R' = 0.01 M, C' = 0.01 μfd.

er is symbolized by a curved-backed triangle; A indicates very high gain, e.g., 10^5 to 10^8. The input of the operational amplifier is to the left and is called the summing junction. The basic principle of such a device is to feedback the output, which is of opposite polarity to the input signal, to the summing junction, so that the feedback current automatically equals the input current at all times. The summing junction will be at virtual ground (± a few microvolts), since an error in summing junction potential is amplified to change feedback current appropriately. If one uses only a capacitor and resistor, as indicated by the heavy R and C, the gain at very high frequencies is very high and the system will usually saturate. This is because any high frequency components in the input see the capacitor as a low reactance. This provides high gain; gain = Z feedback/Z input. It is essential to add,

then, the resistor, R′, which thus limits the response. If, as in the case shown in the figure (upper right), the ratio of R/R′ is 10, the gain at high frequencies asymptotes at a gain of 10. This is quite analogous to the simple RC network, except that some system gain is obtained. Also, $f_c = 1/(2\pi\ R'C)$.

To reduce high frequency noise progressively, in addition to just limiting it, capacitor C′ is added. Such high frequency attenuation can be particularly useful in the presence of FM magnetic-tape-recorder carrier frequencies, radio frequency noise in the environment, e.g., paging systems or TV transmitters, or chopper hash from amplifiers. The most effective system is one in which the time constants R′C and RC′ are equal (9). This is important to maximize the frequency response for the data while minimizing the high frequency noise. In the case shown in Figure 1, this was set at 0.001 sec, giving a characteristic frequency of 1000 radians per second (160 Hz) using the equation:

$$\omega_c = 1/RC' = 1/R'C. \tag{5}$$

This system has a maximum gain, then, of 5 and provides a differentiator with an error of less than 1% amplitude and 11° phase to 16 Hz (at which frequency the gain is 1), and attenuates high frequency noise. By choosing different values of R and C, more gain can be obtained, using the equation:

$$\text{Gain} = \omega\tau = 2\pi\ f\ RC. \tag{6}$$

Other approaches to differentiation are described by Carlson et al (11) and Korn and Korn (12). When the frequency components of the data and noise overlap, a known and fixed frequency response is essential, however. The state variable filter of Kohr (13) can be patched easily on an analog computer and will be described in the section on cardiac output computation (Paper No. 47).

In Figure 2, examples are provided of the derivatives of cardiovascular data using various filters of the type shown. At the top is a trace of the original pressure pulse obtained at the root of the aorta of a dog anesthetized with sodium pentobarbital. The resonant frequency of the catheter-transducer system was over 150 Hz. In panel A, no feedback capacitor was used and the ratio of feedback resistor to input limiting resistor was 100 to 1; f_c = 320 Hz. The noise is obvious. The peak rate of pressure change obtained during the upstroke was about 2550 mm Hg/sec. In panel B, no feedback capacitor was used; f_c = 32 Hz. Although the high frequency noise is greatly reduced, the amplitude of the derivative of the upswing is reduced about 10% and that occurring at the incisura even more. In panel C, the

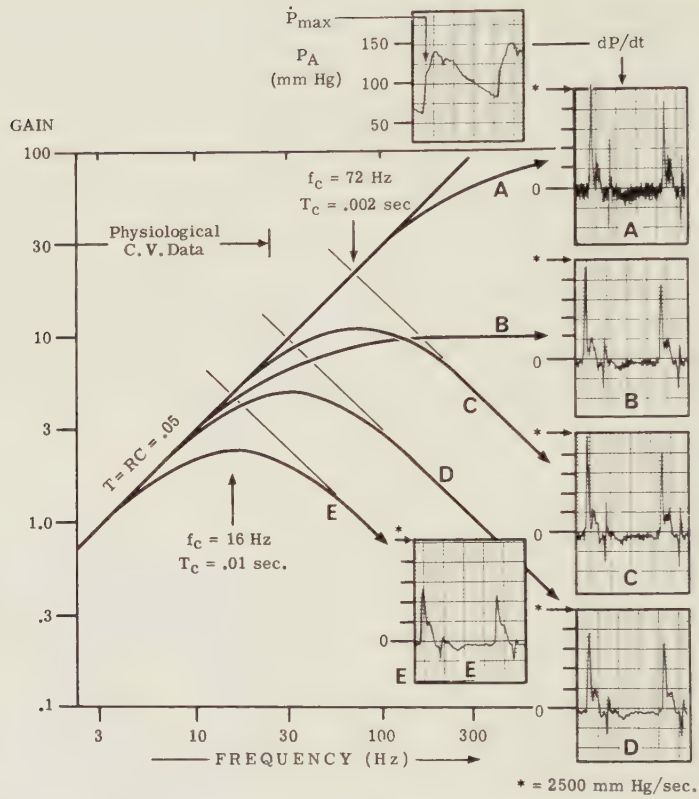

Fig. 2. Examples of differentiation using various filters. Basic differentiation from R = 0.1 M, C = 0.5 μfd, circuit of Fig. 1. In A, R′ = 0.001 M; B, R′ = 0.01 M; C, R′ = 0.005 M, C′ = 0.02 μfd; D, R′ = 0.01 M, C′ = 0.05 μfd; E, R′ = 0.02 M, C′ = 0.1 μfd.

circuit used was similar to that of Figure 2, except the characteristic time constant was 2 milliseconds instead of 1 msec to give f_C = 72 Hz. The derivatives were closer to the values seen without filtering, panel A. In panel D, the time constant was reduced still more, while in panel E, the filtering time constants, R′C and RC′, were only 10 msec, giving a characteristic frequency of only 16 Hz. (Please note the problems likely to occur with simple digital computation of derivatives using 10 msec sampling rates.) Although the pattern is smooth — characteristic of those sometimes seen in the literature — the amplitude of the derivative is but one-half of that seen without significant filtering. The moral of the story: one must be careful in limiting high frequencies, since the desired derivative of complex wave

forms, such as the cardiovascular pulses, by their very nature, contain high frequency components. For cardiovascular data of man and dogs, it seems reasonable to suggest that the characteristic frequency of the high frequency rejection filter be 160 Hz or higher.

In addition to the problems of differentiator characteristics, there are serious pitfalls in obtaining the original signal. Some of these potential hazards are illustrated in Figures 3 and 4. In Figure 3, the derivatives of pressure signals obtained with a compliant transducer (Statham P23AA,

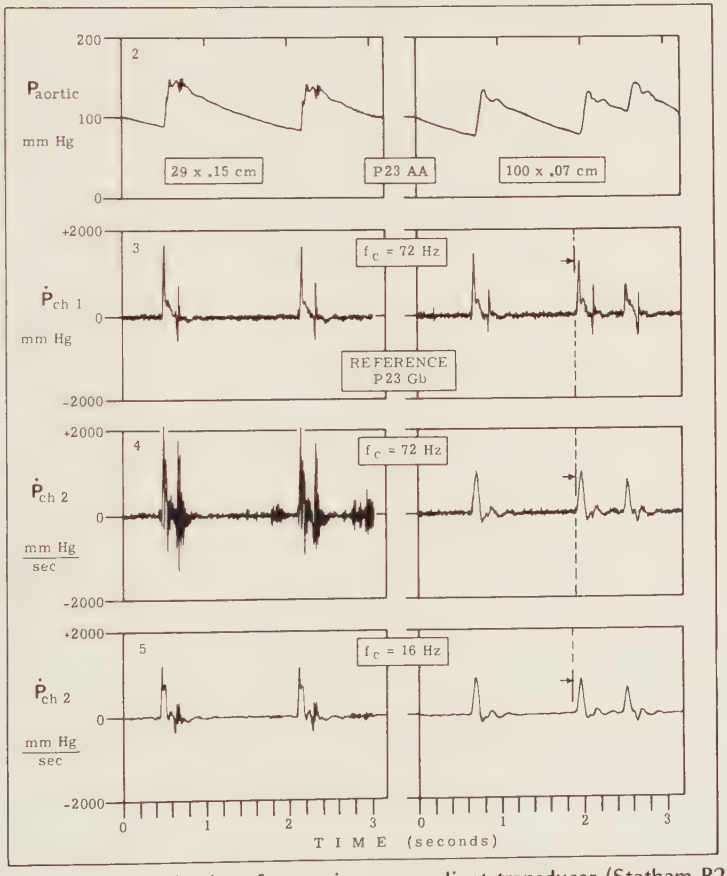

Fig. 3. Erroneous derivatives from using a compliant transducer (Statham P23AA) in comparison to a stiff system (Statham P23Gb). Left: Catheter, 29 cm long, 0.15 cm I.D. Teflon, with tip near the arch of the aorta. Right: 100 cm by 0.07 cm I.D. Teflon catheter on P23AA transducer. Characteristic frequencies of differentiation filters: 72 and 16 Hz using $R'C = RC' = 0.002$ and 0.01 sec, respectively.

channel 4, left panel) are compared to those from a stiff one (Statham P23Gb, channel 3, second row). (Note that the first row corresponds to channel 2, second row to channel 3, etc.). The aortic pressure waveform from an underdamped system, with a system resonant frequency of 42 Hz, is shown in the left panel of channel 2 (top row, Figure 3), and from an overdamped system in the right panel of channel 2. The corresponding derivatives are displayed in channels 4 and 5 (rows 3 and 4) using differentiator cut-off frequencies of 72 and 16 Hz. A good representation of the true pressure pattern is given in Figure 4, channel 1 (left panel). For comparison, the derivative of the signal obtained from the P23Gb reference system using a characteristic cut-off frequency of 71 Hz is shown in channel 3 (Figure 3, second row). Whereas the oscillations of the underdamped system are somewhat obvious (channel 2, left panel), the derivative accentuates the distortion (channel 4, left panel). The peak derivative is erroneously high, in conjunction with continued poorly damped oscillation. If the cut-off frequency of the differentiator is inordinately low, a more attractive pattern is seen (channel 5, fourth row). It should be obvious, however, that in comparison to the more valid derivative (channel 3, second row), such filtering is only misleading. Replacement of the relatively short, large bore catheter by a long one with a small bore produced an overdamped system with disappearance of the added oscillations (channel 2, right panel). However, when the derivatives of the signal from the overdamped system are compared to those from the high quality system (channel 3, right panel) recorded simultaneously, the error is evident. The derivatives with the reasonably high cut-off frequencies (channel 4, right panel) and very low cut-off frequencies (channel 5, right panel) are remarkably similar although high-frequency noise is less evident in channel 5. Because the catheter-transducer system itself reduced the high frequency components, an erroneously low derivative is recorded even with a "good" differentiator system. Note, too, the delay in response, relative to the high quality system in channel 3. Beware!

Slight differences in catheter location can produce significant differences in derivatives. Results using similar catheter-transducer systems are compared in Figure 4. Aortic pressure data for channel 1 (top row) were obtained via the left carotid artery; for channel 2 (second row, left panel) the right carotid was used. In both cases the catheters were advanced, presumably, to the arch of the aorta, yet the configuration of the derivatives (channels 3 and 4, left panels) are significantly different. In the right column, the catheter in channel 2 (right panel) was withdrawn about 10 cm, thus placing it in the carotid artery. In this case, because of the rapid deceleration of blood in the compliant non-linear carotid arteries, in conjunction with a high quality, stiff transducer and a relatively short catheter system, one finds that the derivatives are quite large (channel 4, right

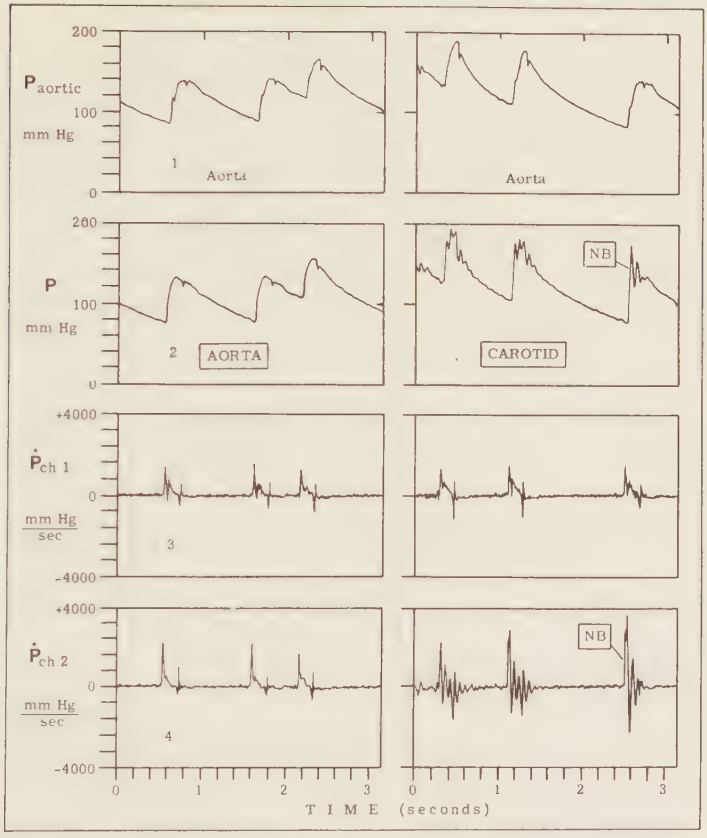

Fig. 4. Different rates of pressure change in different parts of the cardiovascular system. For Channel 1, a P23Gb; for Ch. 2, a P23De; both catheters 29 cm long, 0.15 cm I.D. Teflon. Left: Both catheters about at the arch of the aorta. Right: Catheter in right carotid artery withdrawn about 10 cm into the carotid. Characteristic cut-off frequencies of systems: 72 Hz.

panel). Thus, the highest derivative found in the cardiovascular system may not reside in the ventricle, which is the source of the impulse, but may well be at some other site of the vasculature! It is also important to realize that, in the case of the carotid, the blood vessel was totally occluded by the catheter. Such data are probably not a valid representation of the pressure pattern in the normal carotid!

A final comment relates to the dynamic accuracy of the recorder. If the duration of the maximum rate of pressure rise is short, the derivative will appear as a spike. The recorder must respond both rapidly and without over-

shoot. Recording derivative data on an FM tape recorder and playing back at a lower speed provides a simple means of testing the system.

Digital computation of derivatives is not without pitfalls. In Figure 5, pressure and flow data at the renal artery are presented. The flow was occluded for about 1 sec at 1 sec intervals. The data were digitized at 1

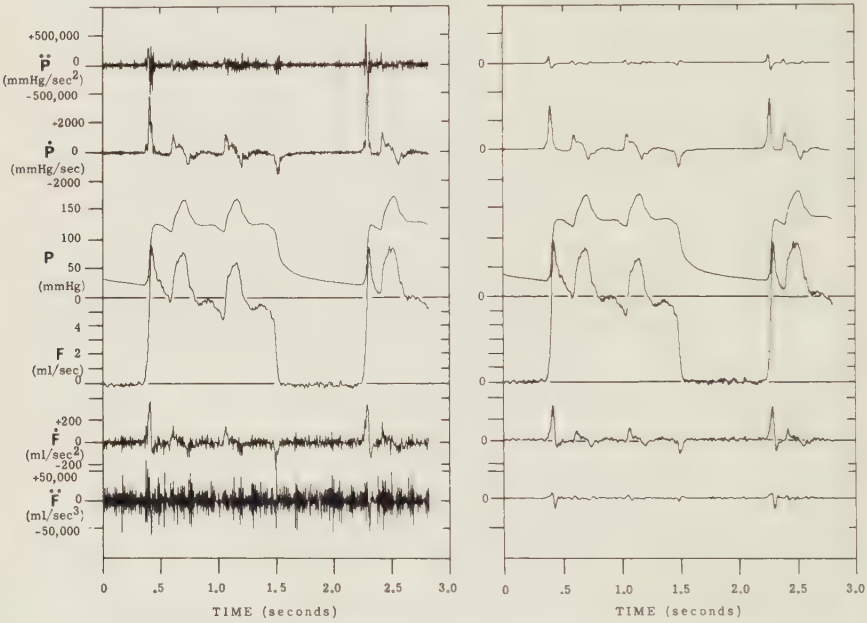

Fig. 5. Digital differentiation of pressure and flow data at the renal artery of the dog. Flow occluded with a pneumatic cuff at 1 sec intervals. Computer algorithms with $\Delta t = 0.005$ sec:

$$\text{Left: } \dot{Y}_i = (Y_{i-2} - 4Y_{i-1} + 3Y_i) / 2\Delta t$$

$$\text{Right: } \dot{Y}_i = (-2Y_{i-2} - Y_{i-1} + Y_{i+1} + 2Y_{i+2}) / 10\Delta t$$

Reproduced, by permission, from *IEEE Transactions on Bio-medical Engineering* BME-19:213, 1972.

msec intervals and 5 values were averaged to provide 200 samples per second. On the left, a simple 3-point interpolating polynomial algorithm (indicated with the legend) was used. Noise was nearly intolerable. On the right, a 5-point, least-squares fit to a parabola was used. Noise was greatly reduced, along with some of the high frequency data, e.g., note the peaks of the first derivatives of pressure and flow.

CALIBRATION OF DERIVATIVES COMPUTATION

Predictable circuits are easily obtainable using quality components, so why waste some of the confidence in the final results and the ease of data reduction by disregard of the calibration factor obtainable from the time constant of the circuit? The system, of course, must be checked by calibration under experimental conditions.

Three general techniques are available to check calibration:

1. *Triangular wave.* If the peak-to-peak amplitude, A, of a triangular wave and the repetition rate or frequency, f, are known, then $1/f = 2t$, and so the rate of change, $\dot{P}$, is: $\dot{P} = A/t$. As an example, in Figure 6, a 4 Hz

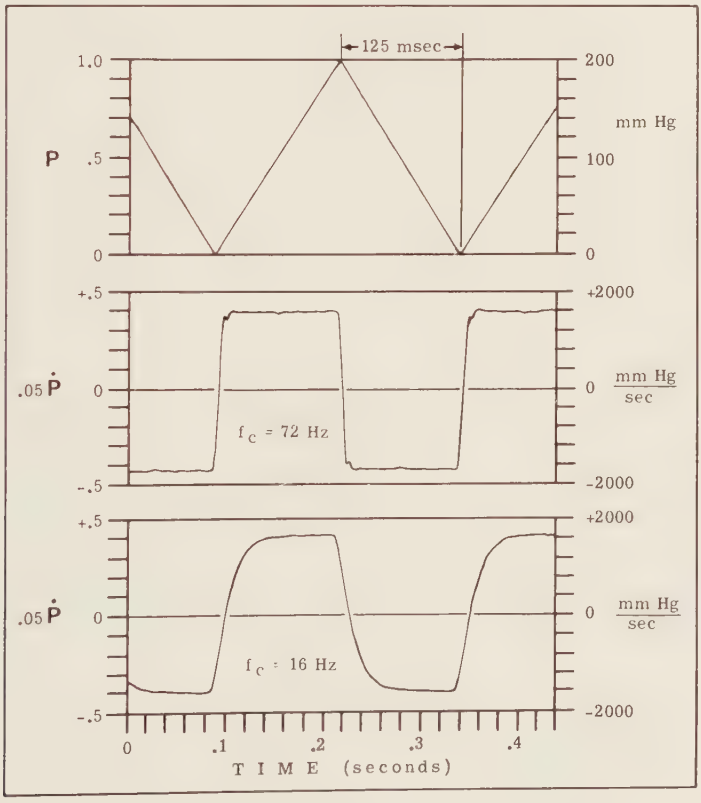

Fig. 6. Use of a triangular wave for calibration.

signal was adjusted to provide a full scale (one scale or computer unit) response equivalent to 200 mm Hg. Since it required ½ cycle (1/8 second) for this to occur, the rate of change of the signal was 8 scale units per second (1600 mm Hg/sec) (top row, Fig. 6). When this was fed into a differentiator with a time constant, and so gain of 0.05, the response was 0.4 scale unit. One should expect this, since 0.05 x 8 = 0.4. The peak-to-peak value of the derivative channel (middle panel) is 4000 mm Hg/sec and may be predicted by dividing the value of the raw data (top channel, 200 mm Hg) by the gain (0.05). As shown in the middle panel, the calibration was indeed valid; zero is at the center. Even with a characteristic frequency of 72 Hz, one sees in this figure that the derivative does not change instantaneously from the positive to the negative value. Even more distortion occurred using the cut-off frequency of 16 Hz, as shown at the bottom of the figure, for over 60 msec were required to attain the true value.

2. *Sine wave calibration.* Since, from calculus, if $y = \sin \omega t$, then $dy/dt = \omega \cos \omega t$, and recalling that $\omega = 2\pi f$, then the peak value of the derivative of a signal will be $2\pi f$ times the signal itself. Thus, the derivative of a 20 Hz, 1 volt peak-to-peak signal should have a peak-to-peak value of $2\pi f$ times 1 $V_{p\text{-}p}$, or 126 $V_{p\text{-}p}$. This example illustrates the amplification problems of true differentiation of high frequencies. As with the triangular wave, the value of the derivative will be attenuated by the factor represented by the time constant.

3. *Calibration from raw data.* If one obtains, with an accurate recorder, a trace of both the raw and differentiated data, a calibration factor may be calculated by scribing lines tangent to the raw-signal-tracing. Using the paper speed to find the time ordinate, and assuming that $dP/dt = \Delta P/\Delta t$, one can calculate the derivative. Here, ΔP is the change in the raw data trace, and Δt is the time required for this change to occur. Because of uncertainties of recorder characteristics, paper speed and, especially, in the "eyeball-fit" of scribing a line parallel to a changing complex pattern, this technique is better for a rough check of calibration, rather than for obtaining the calibration factor to be used in data reduction.

SUMMARY

Morals of this discussion include:

1. The *transducer-catheter system* must have a frequency response uniform beyond that of the data in question. It should have either: (a)

reasonable damping, i.e., ζ = 0.4 to 0.8, and a resonant frequency several times that of the highest frequency of interest, or (b) if damping is low, have a resonant frequency at least 10 times that of the highest frequency, so that high frequency filtering can be used. Reasonable damping is preferred by using fine-bore catheters (14).

2. The *site of measurement* is important, since the acceleration of boluses of blood into the system can lead to interesting, yet distorted, patterns.

3. The frequency response of the *differentiator* must be uniform to at least the highest frequency of interest in the data.

4. The frequency response of the *recorder* must be adequate to detect the derivatives with fidelity.

Errors from any one of the four sources will invalidate the final processed data.

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47. COMPUTATION OF MINUTE-CONCENTRATION FOR CALCULATION OF CARDIAC OUTPUT[1]

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To correct for recirculation in the computation of cardiac output, the decline in dye concentration following the peak is usually assumed to be exponential. Once this exponential decay is underway, it should continue to zero dye concentration, except for the interference of recirculating dye which normally occurs after a period of exponential decay. Thus, the concentration of dye, diluted by the flowing blood, is to be predicted by extrapolation. If the decrease in concentration is exponential, then by definition the rate of change of concentration, dC/dt, during the exponentially decreasing phase is proportional to the concentration:

$$dC/dt = -kC = -\frac{1}{\tau}C \qquad (1)$$

Where: k is the rate constant, and the reciprocal, τ, is the time constant, by definition. The dye concentration as a function of time, C(t), is the integral of Eq. 1, giving:

$$C(t) = C_{t_o} e^{-t/\tau} \qquad (2)$$

For the computation of cardiac output, the minute-concentration (or average concentration over 1 minute of time) is needed. This is the area under the exponential part of the curve to infinite time (the integral of Eq. 2) plus the area (integral) during the early part of the curve. The area under the *tail of the curve,* which is assumed to be exponential, by integration of Eq. 2 is:

$$\text{Area}_{t_o \infty} = \int_{t_o=0}^{\infty} C_{t_o} e^{-t/\tau} dt = C_{t_o} (-\tau) e^{-t/\tau} \Big|_0^{\infty} = C_{t_o} (-\tau)(0-1) = C_{t_o} \tau \qquad (3)$$

where C_{t_O} is the concentration at the instant, t_O, the integration of the tail begins, and τ is the time constant.

[1] These studies were supported, in part, by Public Health Service Grants HE07723 and H6308.

If we can estimate the time constant, we can predict the value of the area under the curve from that time to infinity. Rearranging Eq. 1 gives the desired equation for the estimate, i.e., the ratio of concentration, C, to the derivative of concentration, dC/dt:

$$\tau = -\frac{C}{dC/dt} \tag{4}$$

Substituting the value of τ from Eq. 4 into Eq. 3 gives the desired area:

$$\text{Area under remainder of tail} = C_{t_o}\tau = C\tau = -C\,\frac{C}{dC/dt} = C^2/(-\dot{C}) \tag{5}$$

The area is positive since the derivative of the decaying exponential, $\dot{C}$, is negative. One must also note that the numerical value of Eq. 5 decreases with time, for although τ is constant, the initial concentration, C_{t_o}, for the prediction, is continually changing.

The strategy for computation of the total area under the dye curve is to add this predicted value for the tail, $C^2/\dot{C}$, to that of the integral of the concentration curve starting just before the appearance of dye, t_i, but not necessarily at the moment of dye injection.

$$\text{Total area} = \int_{t_i}^{t_o} C\,dt + C^2/(-\dot{C}) \tag{6}$$

The numerical value of Eq. 6 is meaningless during the early part of the dye curve. However, once an exponential concentration pattern starts, a prediction of the total area to infinite time is available, for the first term provides the integral to that instant in time and the second term predicts the value from that instant to infinity. Of crucial importance to the technique is the fact that, during the exponential decay, as the first term continues to increase, the second term decreases, and thus the sum is constant and is the recirculation-corrected integral. At the moment recirculation begins the value of the second term also increases and the value of Eq. 6 again becomes meaningless. During the interval of exponential decay without recirculation, a value for the total area is thus obtained for computation of cardiac output. If the curve does not have an exponential decay, or if recirculation occurs before the exponential decay is established, there will be no constant value for the predicted total area. An analog readout gives a check of the validity of this important assumption.

COMPUTER PROGRAM

The analog computer program (Fig. 1) was developed for patching an analog computer (Electronic Associates, Inc. Model TR 20). Potentiometer

settings and output values are expressed as the fraction of full-scale. The circuit is a modification of that of Kunz and Smith (1) who used inexpensive operational amplifiers and multipliers of moderate accuracy. The principle is apparently the same as that used in the Lexington Instruments cardiac output computer. Several design features of our modifications are unusual and are of importance (Fig. 1).

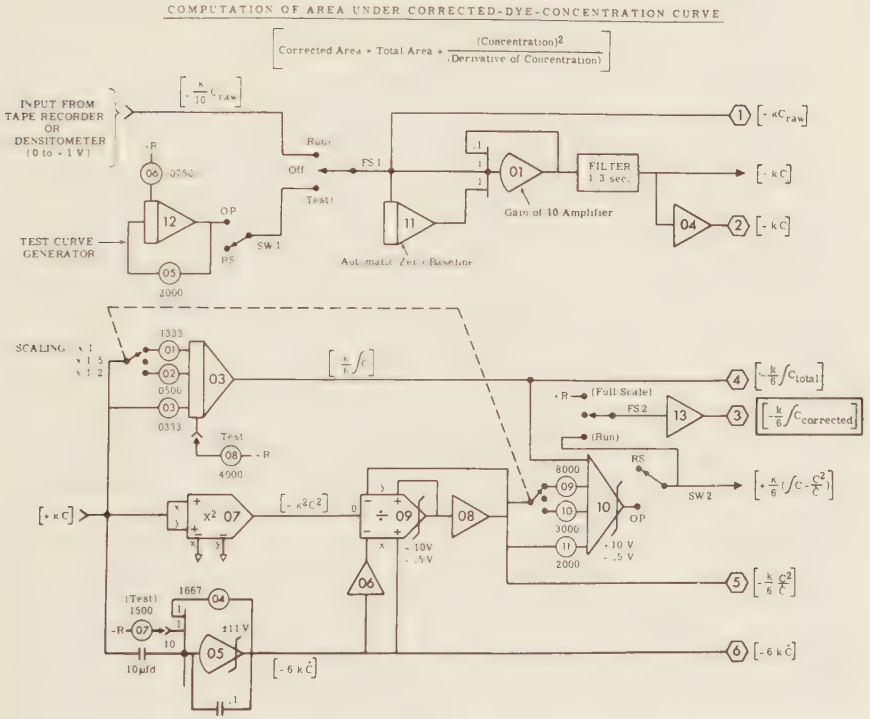


Fig. 1. Analog computer diagram for computation of area under dye concentration curve corrected for recirculation.

A test signal is developed by amplifier 12. The signal is a step increase to 0.075 computer or scale units (where one computer unit, or full-scale, is 10 V) and an exponential decay with a 5-second time constant, like that of Smith and Kunz. This test signal is routinely used to check the operation of the computer at the beginning of each series of runs. The output of A12 and input signals from the recorders are amplified by 10x. Thus, the value of C at t = o with the test signal is 0.75 units. The scaled, predicted total area of the test curve is thus:

$$\frac{1}{6}\,\overline{Ct} = \frac{1}{6}\,C_T = \frac{1}{6} \times 0.75 \times 5 = 0.625 \text{ units.} \qquad (7)$$

The baseline is conveniently and automatically set to zero with amplifier 11. The moment-by-moment value of the concentration is used as an initial condition for this integrator. The output, summed at A01, is subtracted and so cancels the input when the computer is in the Reset mode. However, when the computer is set to Operate (about 5 seconds after the injection of dye and 1 to 3 seconds before the dye appearance), the integrator A11 is in the Operate mode with no input and so at that instant the value of baseline is held constant and is subtracted from the dye curve through the remainder of the computation.

The filter following A01 is critical, for it must pass. with minimum distortion, the low frequency information of the dye curve and yet limit the high frequency pulsations of the heart beat or withdrawal pump which, when differentiated, would lead to fluctuations in the final computed output. The circuit of Kunz and Smith (1) was used, but Analog Devices Model 106 operational amplifiers were used for increased stability (Model 118K would be even better). The values of the resistors were reduced by 1/3 to give a filter of 1/3 second lag. Even with this frequency response higher than theirs, the resulting output values did not fluctuate more than a few percent of full-scale, and the circuit settled more rapidly to provide the predicted value of area than with Kunz and Smith's 1-sec lag filter. Such rapid settling is important if recirculation occurs soon after the peak dye concentration. A zero adjusting control was added to the Kunz and Smith circuit by which current through a 100 megohm resistor string could be applied to the middle amplifier to offset leakage current. Likewise, an adjustable feedback resistor was added to the first stage amplifier for attenuation, since the second stage has a gain greater than 1. Damping must be adjusted so that the overshoot with a step input is zero to not more than 1%. This precludes the use of many 3-pole filter designs which have moderate (5%) overshoot to step inputs (2). Adjustment of overall gain was set to 1.000. The response of the circuit we used is given in Figure 2. The last

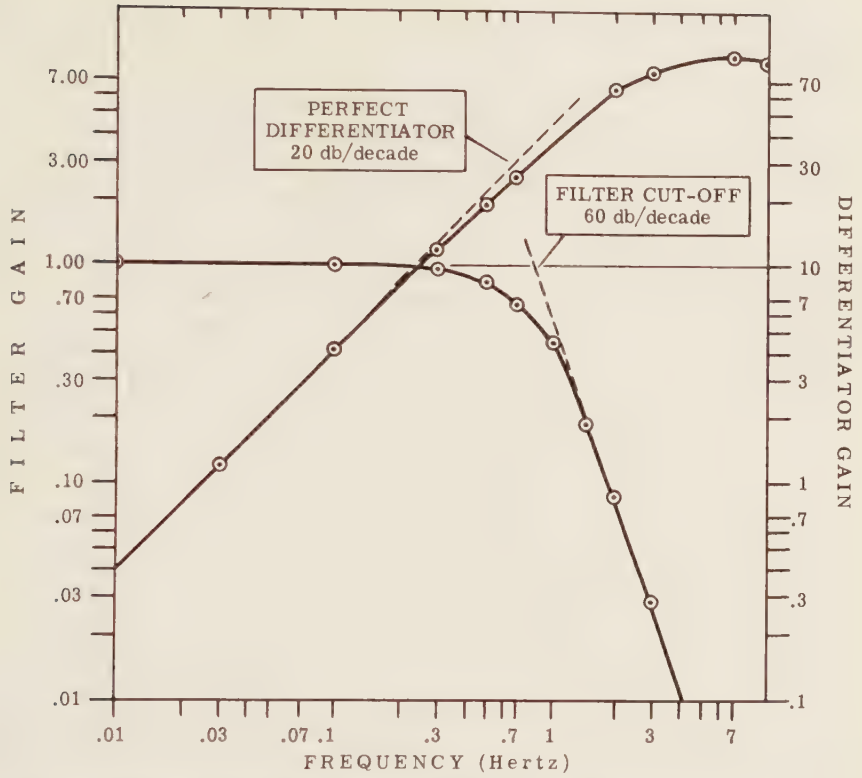


Fig. 2. Frequency response of the differentiator (Fig. 1) and the 1/3 sec lag filter (1) used.

amplifier of the Smith and Kunz circuit was used as a gain-of-one, non-inverting buffer amplifier. The load developing on the amplifier [+kC] is over 8 mA and so a computer amplifier patched to A04 as an inverter was used to supply [+kC]. An operational amplifier with a 20 mA load-capacity is advisable, otherwise.

The high frequency response of the differentiator is limited (Fig. 1) by a feedback capacitor of 0.1 μfd (0.05 μfd would have been better) and an input resistor (10 kohms, preferably 3 kohms) in series with the 10 μfd differentiating capacitor (2). The response of this circuit is also given in Fig. 2. Accurate (± 2% of full scale) predictions were made using the test-signal generator set for as short as a 1-second time constant; most cardiac output curves last for more than 10 seconds.

Switches SW1 and SW2 are borrowed from integrators. They are in the closed position only when the computer is in the Operate mode, and so are

used for developing the test signal and in eliminating the output between runs when the dividing circuit has a divisor of near zero and is fluctuating wildly, or is limited.

Effective operation of the system required limiters on the differentiator and divider to prevent switching transients or division by zero from overloading the amplifiers. These are zener diodes (1N715A) in series with diodes (1N456) placed in opposite polarity and patched between the output and summing junction. In addition, a 20K resistor from the junction of the zener and regular diodes to the appropriate reference voltage supply is used to back-bias the diode and so reduce leakage current (2). A limiter circuit was likewise added to amplifier 10 with a limit at - .5V and +11V to permit setting the recorder at baseline and not having it driven far below scale during the early part of the computations when results are meaningless.

To check patching and initial operation, P07 and P08 are connected to provide check signals.

An example is given in Figure 3. The dog used had a chronic shunt between a carotid artery and a jugular vein (J. Higgins. Department of Medicine, IUMC). The raw data are recorded in Channel 1. The baseline is automatically held at zero about 2.5 sec before the start of the curve. The filter lags the data (Ch. 2) about 1/3 sec. The computed area is shown in channel 3. A plateau lasting about 2.5 sec occurred. Noise is evident. In channel 4 the total integral is shown, while in channel 5 the predicted area to infinity is given from $\dot{C}^2/C$. Recirculation is obvious at 9 sec and so the sum of Ch. 4 and Ch. 5 is no longer constant. The derivative is shown in Ch. 6. About 1 sec is needed for the derivative to settle to a reasonable value; the noise is obvious.

With the shunt open (Fig. 4), the cardiac output proportional to the reciprocal of the area apparently did not change, but recirculation occurred by 6 sec. The plateau was almost non-existent!

If accurate data processing is to be realized, the data themselves must be valid. Thus, for calibration, samples of blood with dye are perfused through the densitometer during the studies. The calibration factor, k, is obtained at the time of the experiment and indicates the response in computer units, U, per mg of dye per liter of blood. As an example, a typical value for a recent series was: k = 0.0863 U per mg dye/L blood, and so 11.6 mg dye/L blood would have given a full-scale response.

To compute the cardiac output, the output of the densitometer (or FM magnetic tape recorder) is used as input to the analog computer program. For typical curves, the scaling required to keep the output of the integrator A03 between 0.2 and 1.0 of full-scale is k/6. That is the scaling factor, k/6, is that coefficient which, when multiplied by the full-scale (or maximum)

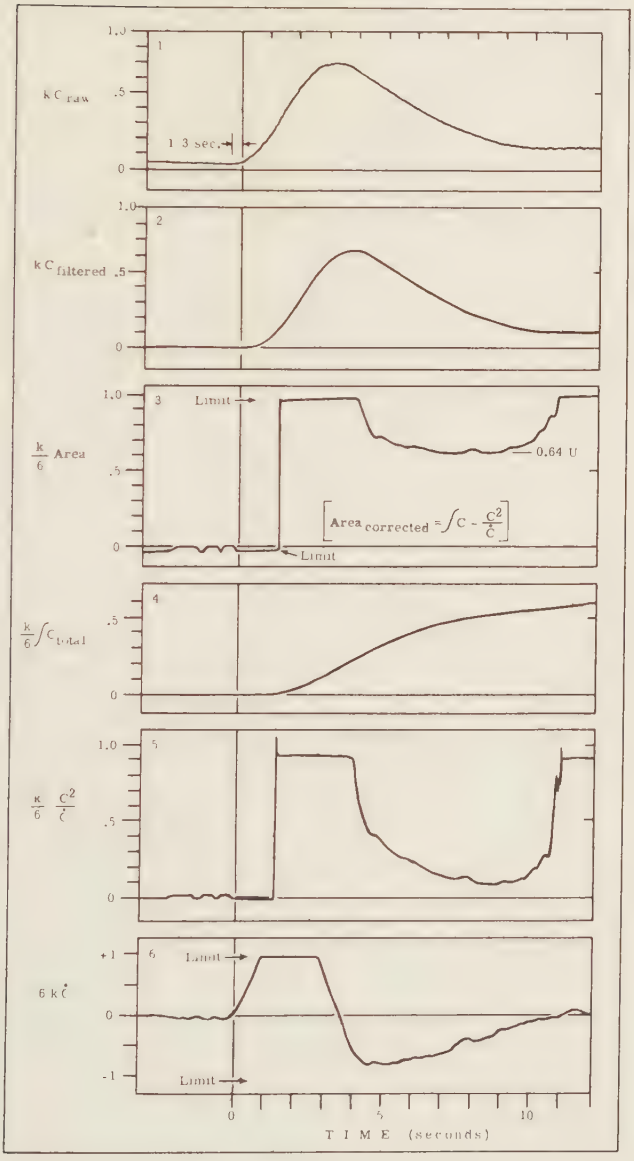


Fig. 3. Results of run showing outputs at points circled by hexagons (Fig. 1). The calibration for channel 2, kC, was such that full scale was 11.05 mg/L.

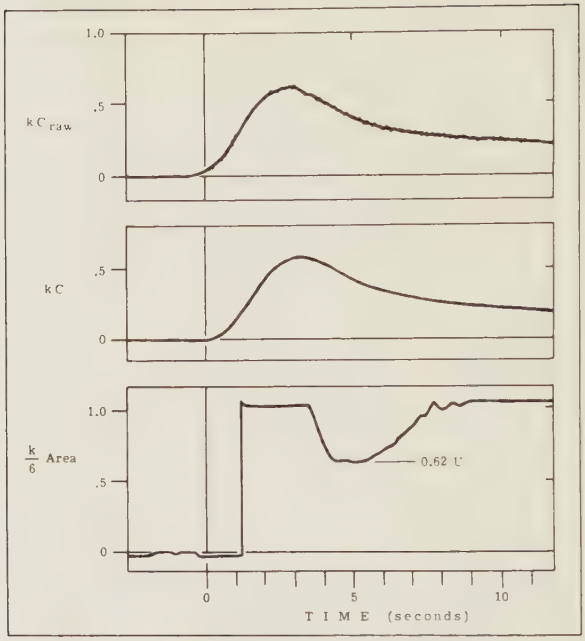


Fig. 4. Dye concentration pattern from dog with open carotid artery to jugular vein shunt.

value of the variable expressed in appropriate units gives a product equal to unity. Scaling and dimensional analysis provide a rational, checkable technique for handling data. Our experience confirms the concept of scaling in which the unit used is the fraction of full-scale (i.e., the computer unit) rather than volts or chart divisions. In our example k/6 is 0.0144, and so full-scale is equivalent to 69.5 mg-sec/L. This provides an output for the corrected-area-under-the-time-concentration curve of [1/6 (k$\int$C)] computer units. Since the computer operates in time units of seconds rather than minutes, the output scaled to be expressed in minutes is: [10 (k$\int$C)] or [10 k $\overline{Ct}$]. Cardiac output is normally calculated using units of mg-liters-minutes. Since the computer output for the recirculation-corrected, minute-concentration is in scaled computer units, it is converted by multiplying by the reciprocal of the scaling factor. Cardiac output is thus:

$$\text{C.O.} = \frac{A}{\overline{Ct}} = \frac{A}{[10\ k\ \overline{Ct}]}\ \text{(in computer units)} = \frac{10k\ A}{Z}\ \text{(in L/min)}, \quad (8)$$

where Z (the area under the curve) is expressed as the fraction of full-scale of the output of A13 during the plateau.

For the example: $A = 1.25$ mg of dye injected

$$k = 0.0863 \frac{U}{mg/L}, \text{ from the example above}$$

$$Z = 0.54U$$

$$C.O. = \frac{\frac{10}{min} \times 0.0863 \frac{U\ L}{mg} \times 1.25\ mg}{0.54\ U} = \frac{1.0787}{0.54} = 2.00\ L/min \quad (9)$$

For multiple determinations the constant coefficients are combined (e.g., 1.0787), and the flow is readily calculated in one operation.

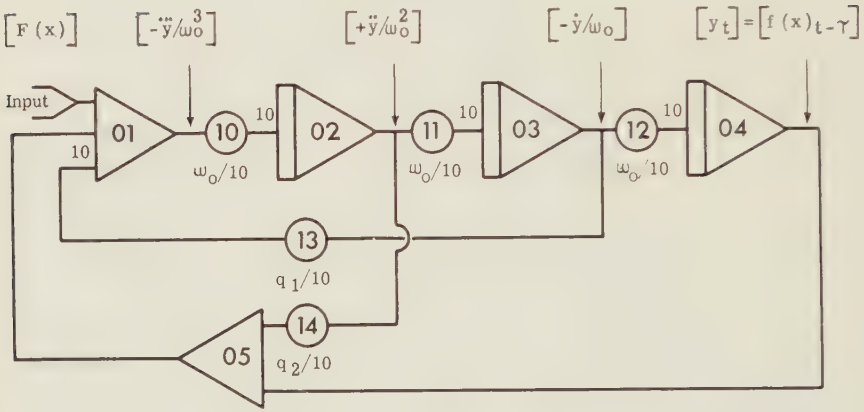
With low flows, the peak dye concentrations at times exceed full-scale. When this is anticipated, the densitometer sensitivity is reduced by a known factor and the indicated area under the curve multiplied by this factor. If the peak value is within full scale, but the area in computer units, $k/6\ \overline{Ct}$, is greater than 1, the analog tape recorder is rewound, the scaling switch of the program set at 1/5 or 1/2 and the indicated area is multiplied by 5 or 2, respectively.

A state variable filter, as developed by Kohr (3) using the coefficients calculated by Paynter, could be used instead of the 1/3 sec filter (Fig. 5) With this circuit, estimates of the first, second and third derivatives are computed, as well as a *transport delay*. By accurately ganging potentiometers 10, 11 and 12, a variable delay system could be implemented for computation of auto or cross-correlation. The frequency response for this transport delay circuit is similar to that shown in Figure 2, if the coefficients (potentiometers 13 and 14, Fig. 5) were changed slightly, as indicated. With these values, the cut-off at the shoulder of the frequency response curve is not as sharp, but the overshoot with a square wave input is reduced. Obviously, no differentiator (Amplifier 05, Fig. 1) is then needed, since the first derivative is available from the state variable filter; gain and polarity inversion are needed.

Hara and Bellville (4) also computed the decay constant and then, at an arbitrary point in the downslope, used it to predict the remainder of the curve by switching to a decay-curve generating circuit using this computed decay constant. The technique suffers from two major faults. First, the switching point must be determined ahead of time—with the method outlined above, all possibilities are used and if none fit, i.e., there is no plateau, then it is obvious. Second, the value of the decay constant is fixed at the instant of switching and with noise it may thus be set seriously in error—with our method the effect of noise is continuously presented, and so may be evaluated.

STATE VARIABLE FILTER, 3rd ORDER

For Analog Computation of Derivatives or Transport Delay



Delay = τ = 0.185 sec.

$1/\tau$ = ω_0 = 5.405 rad/sec

$\omega_0/2\pi$ = f_0 = 0.86 Hz

Coefficients for P13 and P14

Paynter	Rothe
q_1 = 2.145	2.29 to decr. overshoot at 0.10 sec.
q_2 = 1.865	2.02 to decr. undershoot at 0.15 sec.

Fig. 5. State variable filter of the type described by Kohr (3).

With those instruments giving a digital presentation, the user may easily be lulled into complacency by the 3-digit number readout. Our sensory system does not appear to be designed to evaluate a string of rapidly changing digits—thus, the continuing advantage of analog readout, if not computation.

With A/D conversion and appropriate numerical techniques, this program could readily be implemented using a digital computer. Our experience with digital data processing suggests that the problem of obtaining an accurate estimate of the decay constant in the presence of noise will be no easier and but little more accurate than the analog techniques outlined above.

SUMMARY

Calculation of cardiac output from an indicator dilution curve requires a strategy for computing the total area under the curve. The approach described is to add the integral of the concentration curve, starting just before the appearance of dye, to the predicted value for the tail. The total area then is:

$$A_T = \int_{t_i}^{t_o} C\,dt + C^2/(-\dot{C}). \qquad (10)$$

This equation can be solved on an analog computer. The circuit design is described, and several unusual and important considerations are included. This program can also be applied in digital processors if preferred, but the analog technique works just as well.

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48. A PHYSIOLOGICAL DATA ACQUISITION SYSTEM[1]

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Nearly every research worker has some type of data recording system, ranging from the very simple to the very complex, and often customized for the particular research area and available budget. This report describes a data acquisition system for the recording and analysis of data in a cardiovascular research laboratory. As with most recording systems it was not designed initially as such, but came about, over many years, with the addition of new instruments and new requirements and an attempt to integrate them into a useful system.

A block diagram of the system is shown in Figure 1 and a photograph in Figure 2. The experimental animals have usually been larger animals such as the dog, sheep, or primate, used for both acute and chronic experiments. The recorded variables would be pressures, blood flows, respiration tracings, biological potentials, dye concentrations, etc. The system to be described is designed primarily to handle variables ranging in frequency from DC to 100 Hz, and in amplitude from 1 microvolt to 10 volts. Time requirements often cover a wide range: from recording a mean pressure at 30 minute intervals over 12 hours time to the reproduction of events occuring with each heart beat at a rate of 3-4 per second. Because of the need for both of these types of recordings in our research, the system contains some very slow components, such as a mechanical printer, as well as some more rapid units.

The animal is usually placed on the operating table; this was adapted from a human examination table and allows adjustments for vertical height, tilting, and sideways rotation. The cables from the transducers are plugged into a terminal board at the bottom of the table. A 400 Hz square-wave pulse for electromagnetic flowmeter probes and ±15 volts are also available here. No AC line power is connected to the table. The transducer outputs

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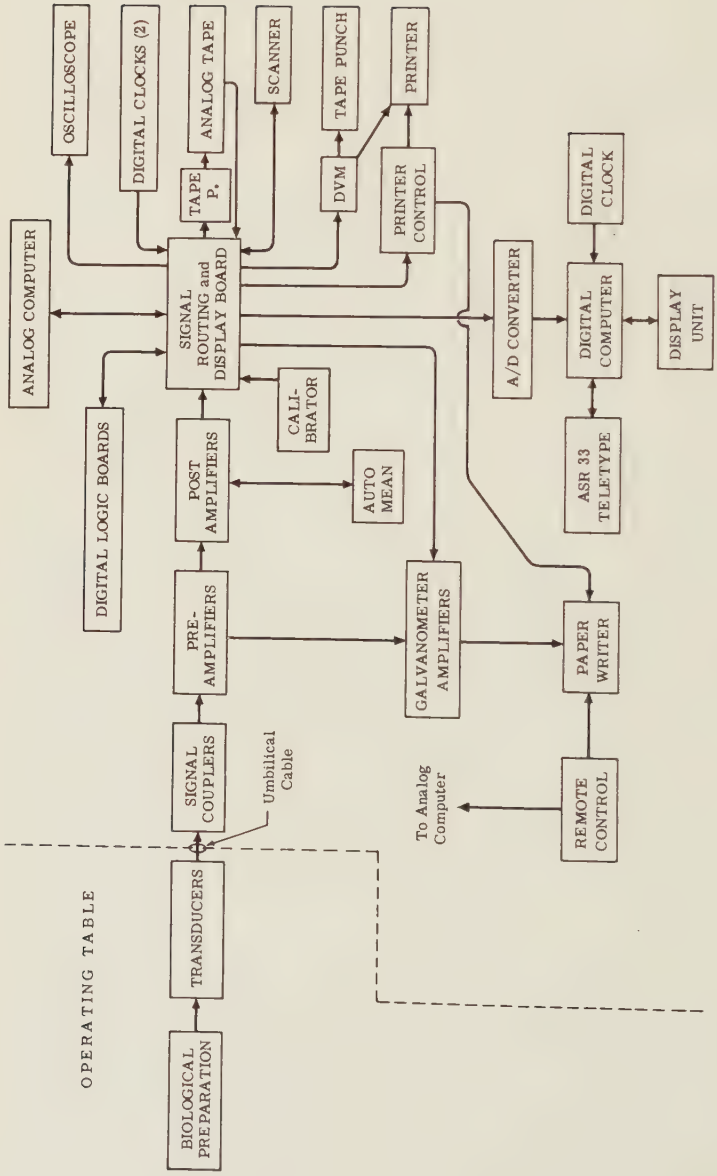

Fig. 1. Block diagram of data acquisition system.

pass, by means of an umbilical cord, to Beckman 481B preamplifiers. The transducer is matched to the preamplifier by a coupler chosen for that transducer. In the case of pressure transducers, calibration circuits are also built into the coupler (Beckman 9872, designed to our specifications). These preamplifiers have a maximum gain of 400, a band width of approximately 0-10 KHz and are stabilized by a 400 cycle chopper. By skipping the input chopper, the output chopper may be utilized to sample the signal from a flowmeter probe.

The output of all preamplifiers is amplified by a postamplifier system of our own design. Basically this consists of PP85A Philbrick amplifiers, which, as utilized, produce a maximum gain of 25 with DC level adjustments (0 to ±1 or 0 to ±10 volts offset) and variable filtering. RC filters are switch-selected for a 3 db attenuation at 10, 30, and 120 Hz. To reduce confusion for the novice operator, only a channel selection switch for a voltmeter and the DC level controls are located on the front panel; the remaining controls are on the rear panel. The postamplifiers are also connected to a rotation cam that actuates a switch to connect a signal averaging circuit; at approximately 30 second intervals the signal may be electronically averaged with a time constant of 3.2 seconds. The investigator may then record an average or mean signal alternating with a pulsatile signal; alternatively, the averaging circuit may be permanently switched on.

The low impedance output of the postamplifiers is available at the signal routing board where pin connections may be made to the appropriate output unit. The signal routing board (Sealectro Corp.) permits pin connections, in an x-y matrix arrangement, of the input signals to any one of several areas: digital voltmeter, analog computer, oscilloscope, A/D converter, magnetic tape, or paper writer. Likewise, as shown in the diagram, signals returning from these devices may be rerouted to the appropriate area. Since each channel is individually routed it is a simple matter to record a channel of the postamplifier on some other channel of the recorder.

The digital computation system consists of a Nova 1200 computer (Data General Corporation) containing 12K of 16 bit word memory (expandable to 32K), an ASR 33 teletype, an eight channel A/D converter, and a display unit (Hazeltine 2000). The display unit is located in the author's office where it may be used for programming or display. When the display unit is used alone a baud rate of 1200 is available for rapid entry and display. When used at 110 baud the output is available both at the display and at the teletype for permanent copy. A switch selects the input device to be used and the baud rate. Future plans calls for addition of a D/A system, fast tape reader, and digital magnetic tape.

Two digital clocks are indicated in the diagram. One of these (Digitec

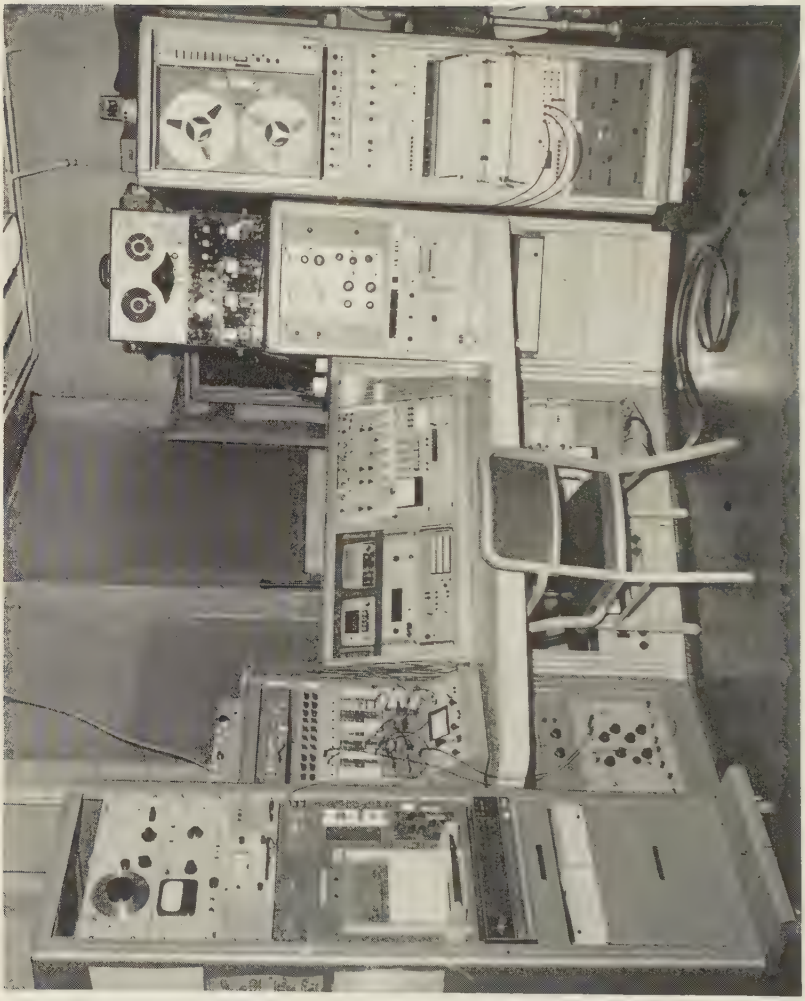

Fig. 2. The system in the author's laboratory. Note umbilical cable to animal table.

661) puts time on the printer (Hewlett-Packard 562A) and also provides an operator-selected 1, 5, 10, 30, and 60 minute signal. This may be used to start the printer and also to turn the paper writer unit from a slow to a fast speed. The timing signal starts a monostable whose "on" time may be adjusted to last from 10 to 120 seconds for paper writer and printer operation. The second clock (Datum 9300) supplies a slow code to the paper writers, and a time code to the digital computer and analog tape recorder. It also reads the analog time on tape playback.

A ten channel scanner system (Digitec 631) may be used to sample at slow rates (up to 10/sec) the outputs from the postamplifiers. The output of the scanner may be used to drive the digital voltmeter (Hewlett-Packard 3440A), and the voltmeter can drive the printer or a tape punch. On the printer the scanned channel is printed along with the voltage and clock time. The maximum printer and tape punch rate is 5 per second. The digital voltmeter and the tape punch unit thus are used as a slow analog to digital converter system. Associated with the printer is one channel of a D/A converter for analog recording.

In the same pullout drawer that contains the signal routing circuits is a power supply and sockets for the plugging in of digital logic circuit boards (Wyle Laboratories). Unfortunately these must be hard wired; semi-permanently wired digital logic circuits are used for multivibrators, gates, relays, and track-hold. On the front panel of this drawer are located push-button and toggle switches to permit the operator to view the output of any postamplifier, analog computer, or tape recorder channel on the digital voltmeter or oscilloscope. Cable connections are made from the rear of this panel to the other racks.

The system includes two paper writers: an 8 channel Beckman Offner Type S and a 3 channel Brush Mark 240. The Brush recorder contains an 8 mm wide channel which is extremely useful for recording important detail in signals with large amplitudes (e. g. ventricular pressure).

Included in the system is a four-channel magnet driver for electromagnetic flowmeters. This instrument has previously been described (1-3). The four channels are essentially identical so that calibration of the probe in one channel results in similar calibration results in any other channel. Thus flow probes are calibrated once for the system and not for the channel being used.

There is no line voltage at the front of the console; a master power switch below the console turns on a 24 volt power supply to operate 24 volt relays. These are turned on by switches at the upper right hand side of the console (Fig. 2). Individual switches are available for the master relay, for the right, left, and center portions of the console, and for an auxiliary bank.

The appropriate power supplies and test equipment are available beneath the console and in the side racks. A large drawer holds the operating manuals, and three small drawers hold most of the necessary cords and analog computer patching equipment. The analog computer is a Pace TR-10 (Electronic Associates, Inc.). It is filled out to the extent of sixteen operational amplifiers, eight integrators, two multipliers, a relay comparator, and an electronic comparator. An additional Model 555 dual set point voltsenser (California Electronics Mfg. Co.) comparator unit has been added; some additional operational amplifiers are also available on another panel. Trunk lines from the signal board go to an input-output panel on the removable patch panel of the analog computer.

A remote control box allows operation of a marker signal and control of the speed of the 8 channel recorder. The remote control also has a reset, hold, and operate switch for the analog computer, along with a jack for a separate hand or foot switch to operate the marker. This allows the operator to stand at the side of an animal, inject a dye, press a foot-operated marker switch, switch the computer from reset to operate to sense the dye concentration (reset being used to subtract any zero offset), and turn the paper writer from a slow to an appropriate recording speed. The same relay system will also actuate the printer mechanism if so desired.

From the signal routing panel, tape signals may be sent through a tape preamplifier to either one of two tape recorders—a Honeywell 8100 with four channels and ½ inch tape, or a home-built three channel recorder, derived from a Viking tape deck, for use with ¼ inch tape. All tape inputs may also be switched to ground or to a one volt calibration signal. Since neither tape recorder has been totally satisfactory, a tape jack connection board (Fig. 2, lower right) is incorporated for use with other recorders. The output of the tape recorders may be played back through the system into the analog computer or paper writer as desired. Two channels may be simultaneously displayed on the Tektronix 502 oscilloscope.

SUMMARY

A physiological data acquisition system for use in cardiovascular research in larger mammals is described. Transducer amplifiers, paper writers, an analog and a digital computer are interfaced for efficient operator observation and manipulation of the recorded data.

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49. PROCESSING OF PHYSIOLOGICAL DATA AND SIMULATION OF BIOLOGICAL SYSTEMS IN AN ANALOG COMPUTER WITH PARALLEL DIGITAL LOGIC

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Computing machines provide a most powerful tool for analysis and interpretation of biological problems. Variables can be submitted readily to sophisticated operations of algebra and calculus. Conceptual models of living systems can be embodied into mathematical expressions which, in turn, can be mechanized for solution in computing machines. Because of this potential to augment the acquisition of knowledge and understanding, computers will play an integral role in the work of life scientists. Therefore, a natural question can be posed as to what type of computers are most adaptable to the needs of biological workers. Analog computers, digital computers, hybrid computers? Obviously, there is no simple answer to this question and we will limit our discussion to a brief presentation of the salient features of each machine as well as to an account of our own experiences with their application to some specific problems. We will also give some consideration to such factors as simplicity and flexibility of operation, cost, and integration of man and machine during the process of learning.

CYBERNETICAL AND PRACTICAL CONSIDERATIONS

Analog Computers

The output signals of most physiological transducers appear as continuous voltages which are analogous to such physical quantities as pressure, flow, volume, etc. Thus, cybernetically, analog signals are the natural currency for most transactions between physiological workers and the living systems they study. Similarly, in an electronic analog computer, physical quantities are represented by levels of voltages. The mathematical operations of addition, subtraction, multiplication, division, integration, differentiation, etc., are performed on these voltages by active linear and non-linear circuits. The operations are performed continuously and

almost instantaneously (nanoseconds), even when the voltages themselves are changing rapidly. What is more important, many operations in a problem are executed simultaneously, e.g., the instantaneous difference between two quantities can be divided by the instantaneous value of another quantity and the result, in turn, can be integrated, differentiated, squared, etc. These simultaneous results can be plotted separately in the form of analog signals in different channels either in the time domain or in other systems of coordinates, (e.g. x-y plane), as the problem is being solved. Because of the familiar format of this information, many physiologists and other life scientists take a rapid liking to analog computers.

Much of the power of analog computers resides in their ability to solve non-linear differential equations, a capability extremely well suited to the study of living systems where non-linearities prevail. There are other advantages in the use of analog computers by life scientists. Programming is generally straightforward and numerous changes can be rapidly and directly introduced in the programs. Different parts of the program can be addressed as the computation proceeds toward a solution and this capability is closely related to the process of learning and to a successful man-machine integration. With the addition of parallel digital logic, computation components such as "and" gates, "or" gates, downcounters, monostables, etc. become available and add greatly to flexibility of operation. Thus, it becomes possible to control independently the operation of selected integrators. For example, one can restrict the integration of a quantity of interest to the phase of isovolumic contraction in a cardiac cycle. Then, one can set a downcounter to any number of cycles between one and 99, and have the integrated quantity for each cycle stored in a track-and-store component. The final result can, in turn, be divided by the number of cycles selected, and the average value per cycle of the integrated quantity of interest can be immediately displayed. Many other similar operations can be solved in an analog computer when parallel digital logic is available.

The question of cost is something of a moot matter. However, it may be fair to say that, for equivalent power, analog computers are less expensive than digital computers. This may be particularly true for smaller installations where there is no full use of computer time.

There are also disadvantages associated with the use of analog computers. Their accuracy is less than that of digital computers. All the same, physiological signals themselves are not very accurate. Perhaps the most troublesome difficulty concerns the need for painstaking scaling of all variables. It is usually frustrating to attempt to solve a problem after a supposedly correct scaling to find that the only answer given by the com-

puter is an array of lighting overload lamps. Special methods such as careful "static checks" may reduce these difficulties.

Digital Computers

In a digital computer, physical quantities are represented in the form of discrete numbers which are operated upon directly. The basic operations in these machines have the form of binary or octal counting of electrical pulses. In a typical installation for physiological data processing, the analog signals from transducers are converted into numbers using an electronic analog to digital converter (A/D). The basic mathematical operations are programmed in the form of a set of instructions written in an intermediate language such as FORTRAN, ALGOL, COBOL, etc. These instructions are transformed into machine language by a special compiler program. The machine operates on the discrete instructions sequentially and the intermediate results are stored in the computer memory. The speed of the computation depends upon the access time to the memory, the size of the memory itself, and the switching speed of the computer. The accuracy of the computations is theoretically boundless, constrained only by the precision (number of digits) to which a number is represented in the calculation.

Clearly, an uninitiated life scientist will find nothing very familiar in the statements above. This is perhaps the main difficulty in using digital computers to solve biological problems. The prospect of learning strange languages and their transformations are, at the least, not appealing. It can be said that the scientist may limit himself to formulate the problem and leave the rest of the task to experienced "programmers" and operators. This is true, and is done in many cases. Success is almost guaranteed if what is needed from the computer is a mere bookkeeping operation. However, if the problem involves conceptual aspects, this approach introduces a gap in the natural process of learning. If the solution is correct, or at least consistent with conceptual predictions, all may still be well. On the other hand, if the solution is not correct, it becomes almost impossible to find where our reasoning has been faulty. This is due to the particular way digital computers operate. Once the problem has been introduced into the machine by one method or the other, and after the operation begins, the inexperienced scientist loses contact with the computer. To him, the machine seems to withdraw into itself without giving indications as to what it is doing. After some time, he will get an answer printed in neat columns or displayed in some device. If the answer does not seem correct, he can ask for the introduction of some changes and request a new computational run. Although

the machine has ways of indicating errors in programming or illegal mathematical operations, it has no means to tell where conceptual reasoning has been faulty. This is true also for analog computers but there, the solution is continuous in time and changes introduced during the run itself appear immediately in the results. This is particularly useful when operating the analog computer in repetitive operation, and provides for a better chance to uncover conceptual errors in the thinking process.

All that has been said about digital computers does not apply to those gifted life scientists with a solid background in higher mathematics and computational sciences. They can handle their own programs and interrogate digital computers in many ways without need of intermediate programmers and operators.

Hybrid Computers

Systems composed of linked general purpose analog and digital computers, or true hybrid computers, are the most powerful tool available to investigators. They combine the advantages of both systems and tend to minimize their disadvantages. Such combinations have made possible the high rate of success of space flights. Nevertheless, true hybrid computers are not easy to handle. We have used them to some extent to optimize parameters of a model of venous return to the right heart (1), but, except for straightforward bookkeeping problems, we recommend that their extensive usage be left to those who can more readily afford the financial and intellectual cost of their operation.

Analog computers with parallel digital logic, although also called hybrid computers, do not qualify in the category of the systems described above. Here, the logic levels are not numbers but prescribed voltages representing the state of the components: logic one and logic zero. Their operation does not require the sophisticated skills necessary for that of true hybrid computers.

APPLICATIONS OF THE ANALOG–PARALLEL DIGITAL LOGIC COMPUTER

We present two examples of the application of analog-parallel digital logic computations as used in our laboratories. The first concerns the characterization of the contractile state of the myocardium. Although the computer increased our conceptual understanding of the problem in the initial phases of the investigation, this is primarily a bookkeeping operation. The second relates to the analytical solution of the pressure-volume relationships in veins and other thin-walled tubular structures.

Characterization of the contractile state of the myocardium. Through thermodynamic considerations (2), we had arrived at the conclusion that the contractile state of the myocardium can be defined during the phase of isovolumic contraction by the change in free energy, i.e., the potential to do work. Two quantities were required for this definition: the mean power density (MPD) and the mean rate of generation of power density (MRPD). In other words, "how much" and "how fast" power is being made available by the isometrically contracting muscle.

The equations to be solved were:

$$MPD = \frac{1}{p_{max}} \int_0^{p_{max}} \dot{p}\, dp \qquad (1)$$

where p_{max} is the maximal isovolumic ventricular pressure and ($\dot{p} \equiv dp/dt$) and

$$MRPD = \frac{1}{\dot{p}_{max}} \int_0^{\dot{p}_{max}} \ddot{p}\, d\dot{p} \qquad (2)$$

where $\dot{p}_{max}$ is the maximal isovolumic dp/dt and ($\ddot{p} \equiv d^2p/dt^2$).

The continuous solution of equations (1) and (2) during the experiments were to be displayed in the x-y plane on the screen of an oscilloscope and also be available for numerical readout in the digital voltmeter (DVM) of the analog computer. Signals available "on line" or from analog magnetic tape recordings were: left ventricular pressure (P_{LV}); aortic pressure (P_{aort}) and electrocardiogram (ECG).

Figure 1-A shows a block diagram of the arrangement of the instrumentation in our laboratories. The shaded boxes represent the true hybrid linkage which is not germane to the present discussion. Figure 1-B shows displays on an oscilloscope of the quantities MPD and MRPD, before and after the administration of isoproterenol to a dog. Figure 2 presents the analog computer program used to solve the problem, and Figure 3 shows the logic circuits and the timing diagrams. Symbols representing computer elements are drawn according to standards set by Simulation Councils, Inc.

Because an electronic analog computer can integrate only with respect to time, a change in variables became necessary, and equations (1) and (2) were solved as:

$$MPD = \frac{1}{p_{max}} \int_0^{t} \dot{p}^2\, d\tau \qquad (1')$$

and

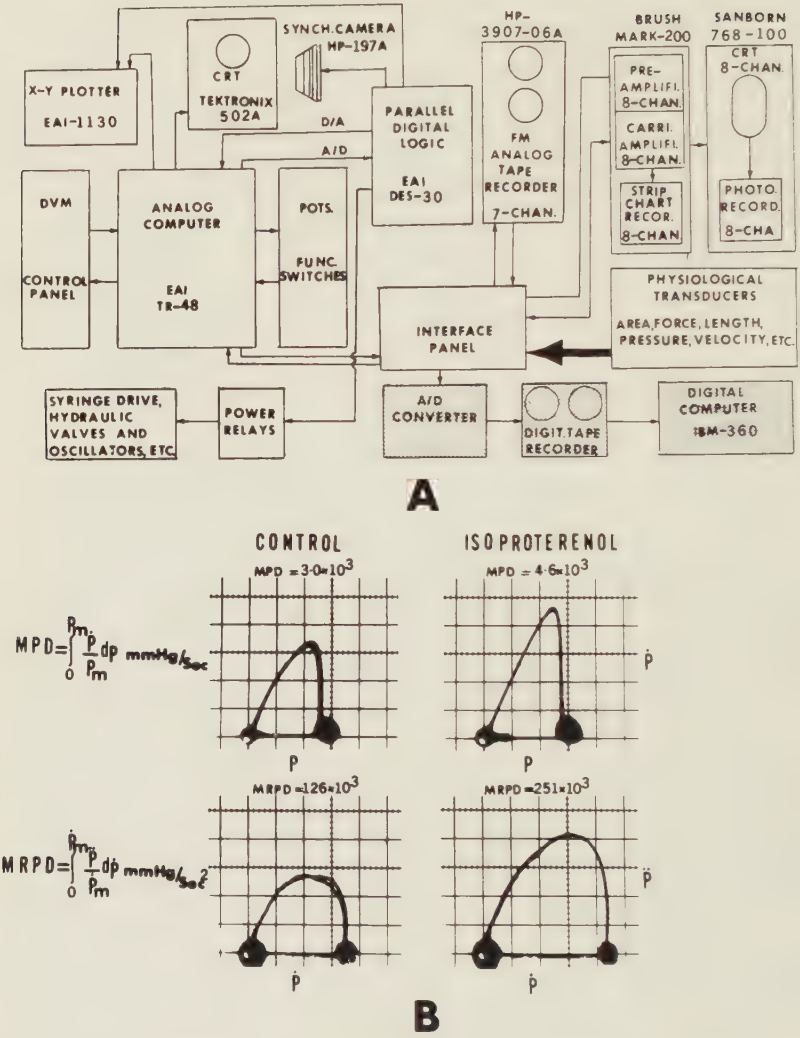

Fig. 1. (A): Arrangement of instrumentation in our laboratories. Shaded boxes represent true hybrid linkage not used in this discussion. (B): Oscilloscope displays in the x-y plane of mean power density (MPD) and mean rate of generation of power density (MRPD) in the myocardium of a dog before and after stimulation.

$$MRPD = \frac{1}{\dot{p}_{max}} \int_0^t \ddot{p}^2 \, d\tau \qquad (2')$$

where t=0 is the beginning of isovolumic systole and t is the time of opening of the semilunar valves.

On the middle section of the left side of the program in Figure 2, the scaled left ventricular pressure ($p_{LV}/100$) from the carrier amplifier or the

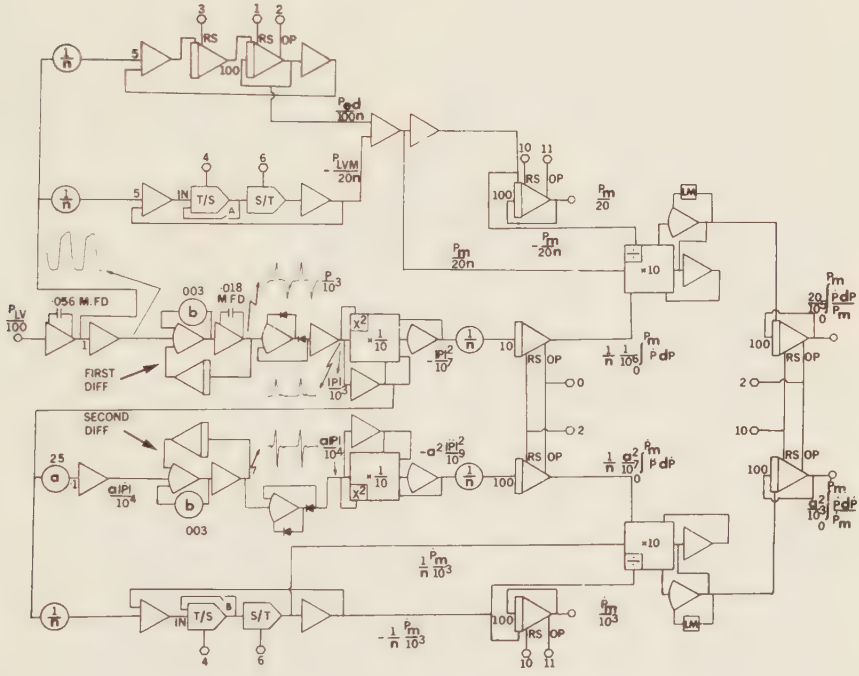

Fig. 2. Analog portion of the program to obtain the quantities MPD and MRPD (see text).

analog tape is introduced into the computer. High frequencies from the carrier oscillator, tape noise, etc., are filtered by the small capacitor across the first amplifier. After diminishing the gain by a factor of 10 in the second amplifier, the scaled first time derivative is generated by the high gain, three-amplifier, differentiating circuit. An absolute value circuit eliminates the negative part of the derivative. Then, $\dot{p}^2$ is generated by a squaring card. Before continuing in this direction, note that $|\dot{p}|$ also proceeds downward in the diagram, passes through a potentiometer containing a scale factor (a), then through an amplifier which reduces its gain by a factor of 10, and enters a second differentiating circuit were $\ddot{p}$ is generated. Again, after an absolute value circuit, p is squared. Note now, that $\dot{p}^2$ and $\ddot{p}^2$ are divided by potentiometers containing (1/n), where n is a constant representing the selected number of cycles over which the next integration will be performed. Next, $\dot{p}^2$ and $\ddot{p}^2$ are integrated over the prescribed number of cycles. Note that the integrators are controlled by logic signals appearing in terminals 0 and 2. These signals restrict the integration to the isovolumic phase of each cardiac cycle. Before elaborating on the generation of the logic signals, we need to complete the description of the analog program. Returning to the amplifier where ($P_{LV}/100$) is introduced, we see that before entering the amplifier with the gain 0.1, the signal proceeds also in the upward direction. Then, it passes identical potentiometers (1/n) to reach two circuits that, although having different configuration, perform similar track-and-store functions. One of these circuits, controlled by logic signals at terminals 4 and 6, renders the negative value of the maximum isovolumic ventricular pressure. The other, controlled by logic signals 1, 2, and 3, produces the positive value of the end diastolic ventricular pressure. The outputs of both circuits are then subtracted to obtain (p_{max}). This value is displayed, at the end of the prescribed number of cycles, in the accumulator controlled by logic signals 10 and 11. It also enters, as the divider, in the division circuit where the previously integrated value of p^2 isovolumic enters as the dividend. We can note now, that a similar process is taking place in the lower part of the diagram. If we take p just before it enters the scaling potentiometer (a), we see that it also proceeds downward toward a potentiometer (1/n), to then reach a track-and-store circuit controlled by logic signals 4 and 6. The output of this circuit renders the value of p_{max} which is displayed in the accumulator controlled by logic signals 10 and 11. As in the case of (p_{max}), ($\dot{p}_{max}$) also enters as the divider into a division circuit where the previously integrated value of p^2 enters as the dividend. We see now that symmetrical accumulators controlled by logic signals 2 and 10 display the scaled solutions to equations (1) and (2), solved as equations (1') and (2').

Figure 3 shows the circuits generating the logic signals and their corresponding timing diagram. In the upper left part of the illustration, we see the scaled variables ($P_{LV}/100$) and ($p_{aort}/100$) being subtracted and filtered to the same extent as in the program in Figure 2. When the value of the subtraction equals zero, at the time of opening of the aortic valve, the

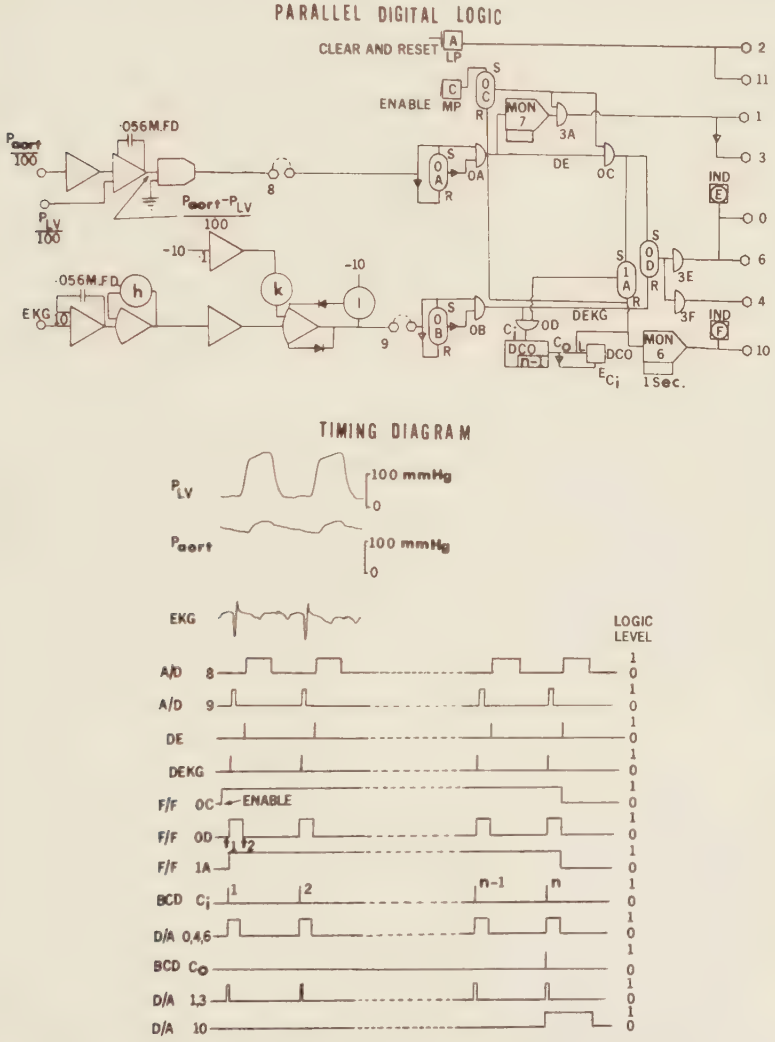

Fig. 3. Parallel digital logic controlling program in Figure 2. The lower part of the illustration shows the timing diagram.

comparator generates a signal that triggers the logic circuits indicating the end of isovolumic systole. Similarly, in the lower part of the illustration, the electrocardiogram signal (ECG) is introduced and filtered to the same extent as the pressures. The main component of the QRS complex is shaped to a sharp spike by the "bang-bang" circuit shown as an amplifier with diodes and potentiometers. This signal is used by the logic circuits to determine the length of computation of several variables, i.e., ventricular end diastolic pressure (from the spike to the number of milliseconds set by monostable number 6), $\dot{p}^2$ and $\ddot{p}^2$, p_{max} and $\dot{p}_{max}$ (during isovolumic contraction), etc.

The downcounter (DCO), sets the number of cycles (n-1) over which the computations will be averaged. Flip-flops and "and" gates complete the circuitry. Monostable number 7 resets all circuits for a new computation, once a run of the prescribed number of cycles is completed. Its setting at one second, shown in the diagram, is arbitrary.

Analysis of pressure-volume relationships in veins and thin tubes. Thin-walled tubes, when surrounded by ambient pressures of the same order of magnitude as their internal pressure, offer peculiar pressure-volume and pressure-flow relationships. In the neighborhood of zero transmural pressure ($\hat{P}$)*, the relationship acquires its greatest interest, and, for years, it has been treated empirically, i.e., using function curves obtained from experiments. In this region, bending is the primary mechanism for change in cross-sectional area of the tubes. The cross-section varies from flattened to oval or circular configurations. An elaborate set of equations describing this mechanism has been derived and solved in a digital computer by Kresch (3). The theory of elasticity offers a simpler governing equation to describe the change in curvature of an annular section of the tube submitted to different transmural pressures.

$$\kappa = \frac{\hat{P}}{2EI} r^2 + \text{const.} \qquad (1)$$

where κ is the change in curvature; $\hat{P}$ is the transmural pressure, E is the modulus of elasticity; I is the moment of inertia ($I = h^3/12$, where h is the thickness of the wall); the product EI is the modulus of flexural rigidity; and r is the distance from a special origin (the axis of the tube) to a point in the cross-section of the annulus; for the special case of a circular cross-section, r equals the radius of curvature.

Equation (1) has been solved in an analog computer by Katz and Chen (4). In our laboratories we made extensive comparisons of computer solu-

* $\hat{P} \equiv$ inside pressure minus outside pressure

tions and experimental results in thin latex tubes and in veins (5). The solutions for latex tubes occurred, as in the experiments, at constant perimeter, i.e., only bending of the walls was taking place. For veins, with much smaller EI, solutions could be obtained in the computer only if the perimeter was allowed to change. Surprisingly, the amount of change in perimeter necessary to obtain a solution for a given transmural pressure was exactly the same as that measured in the experiment of the same pressure. The experiments indicated that with such a small modulus of flexural rigidity as that of veins, a subtle combination of bending and stretching determines the deformation of their walls for changes in pressure in the neighborhood of zero $\hat{P}$**. Clearly, nature may have provided this combination to avoid abrupt changes in compliance such as those observed in latex tubes. What was not clear, is how an equation derived to describe inextensional bending would give solutions with changes in perimeter equivalent to those observed experimentally. It seemed that the computer knew something about the equation that we did not know. We incorporated this thought in our report, but understandably, the editors did not find it acceptable as part of a scientific article. As it happened, there was an element of truth in our statement. The equation was derived by the elasticians to solve the problems of more solid structures where stretching was not expected or even desired. One year later and, after considerable theoretical work (6), it became apparent to us that the phenomenon of stretching was incorporated in the constant in equation (1) where the elasticians had "lumped" quantities that were negligible for the cases they were studying. It was, then, possible to derive a set of more refined equations that would predict the combination of bending and stretching in the neighborhood of zero $\hat{P}$ for tubes of such a small EI as veins.

The new set of equations can be summarized as:

$$\ddot{x} = -\dot{y}\,\frac{\kappa(s)}{1+\epsilon_\theta(s)} \tag{2}$$

$$\ddot{y} = \dot{x}\,\frac{\kappa(s)}{1+\epsilon_\theta(s)} \tag{3}$$

and

$$\kappa(s) = -\frac{\hat{P}}{2EI}(x^2+y^2) + \frac{\hat{P}}{2EI}\,y^2(o) + \kappa_o(s) + [1+\epsilon_\theta(o)]\,\ddot{y}(o) - \ddot{y}_o(o) \tag{4}$$

**It should be kept in mind that the analysis is confined to this region. When veins or thin tubes are fully inflated to their circular cross-section, any further inflation deforms their walls by the simpler process of pure stretching. This is the case for arteries and other thicker tubes which retain their circular cross-section even when they are empty.

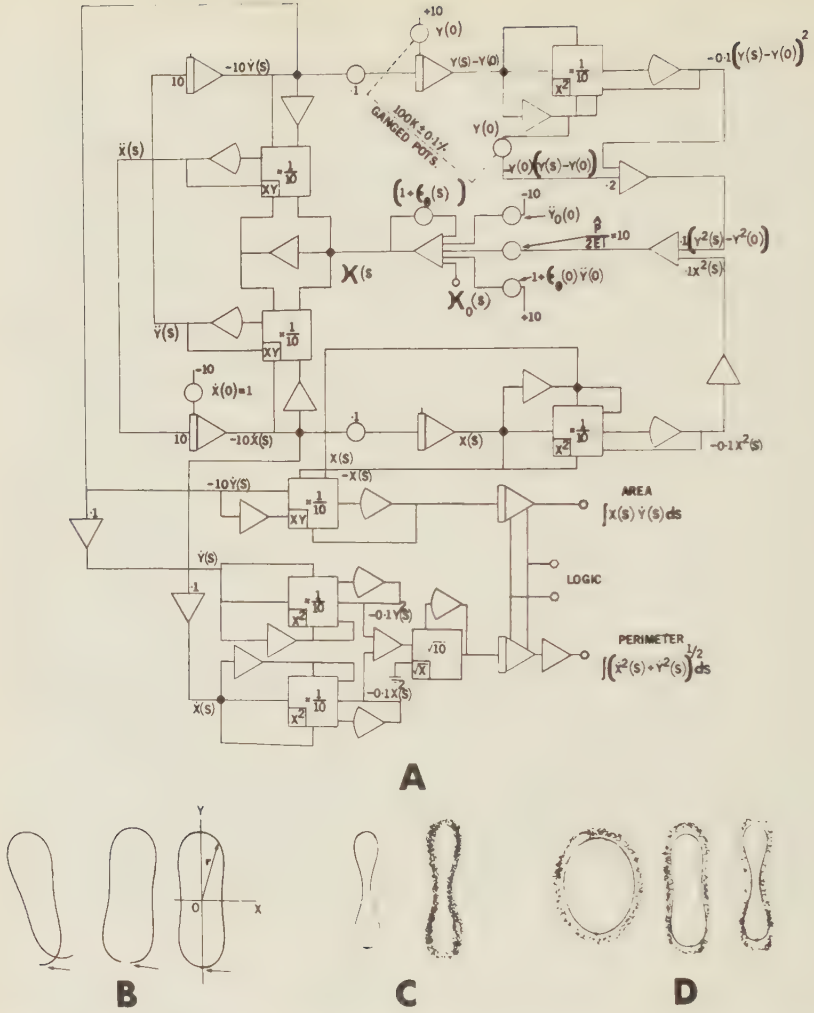

Fig. 4. (A): Analog-parallel logic program for simulation of deflection of the wall of veins and thin tubes under the effect of a transmural pressure ($\hat{P}$). The program solves a fourth order, symmetric, non-linear differential equation in the x-y plane. From the symmetry of the problem, and given values of $\hat{P}$, E, and I, the only unknown is the initial condition y(o). This is obtained by adjusting the ganged potentiometers shown in the upper middle part of the program. $k_o(s)$ is the initial curvature which is arbitrarily selected, i.e., oval, ellipse, etc. (B): Approaching and reaching a solution. (C): Comparison of a computer solution and experimental contour from cinefluorography for equal values of transmural pressure. (D): Several solutions and experimental contours (superimposed) for corresponding values of transmural pressure.

where $\kappa(s)$ is the curvature at the midplane of the annulus, $\epsilon_\theta(s)$ is the strain at the midplane; (s) is the perimeter of the annulus at its midplane; $(x^2 + y^2) = r^2$; x and y are the coordinates of the annulus in the x-y plane; $\dot{x},\dot{y},\ddot{x},\ddot{y}$, are derivatives with respect to (s); $k_o(s)$ is the curvature along the perimeter at $\hat{P} = 0$; y(o) is an initial condition to be solved; and $\ddot{y}(o)$ is a constant equal to the curvature $K_o(s)$ at $s_o = 0$.

For veins, $\epsilon_\Theta(s)$ is finite, whereas for latex tubes, it is negligible. What is truly remarkable is the capability of the computer to give the correct results even when the explicit solution of the equation was not supplied to it. Furthermore, if it were not for the persistence of the computer in giving us a solution that we had not anticipated, we probably would not have become aware of the possibility of obtaining an explicit solution.

Figure 4 shows the analog program. Note that by symmetry, $\dot{y}(o) = 0$ and $\dot{x}(o) = 1$. The problem is to find a closed loop solution for different values of $\hat{P}$ and given values of EI, $\ddot{y}(o)$ and $k_o(s)$. The solution is obtained by adjusting y(o) using the ganged potentiometers shown in the upper middle part of the program.

SUMMARY

Analog and digital computers are rapidly becoming an integral part of the modern physiological laboratory. Here we take the point of view of the physiological investigator who was not primarily trained in the use of the tools of physics and mathematics, and give his reaction after a first encounter with these computing machines. We submit that analog signals are the natural currency for most transactions between physiological workers and the living systems they study. Therefore, many physiologists and other life scientists tend to feel more comfortable when using analog computers. On the other hand, digital computers appear to physiologists as a more reserved type of machine. Strange intermediate languages contribute to this impression. Except for the case of mere bookkeeping operations, the uninitiated life scientist finds nothing very familiar in the ways of a digital computer. We then discuss the advantages and disadvantages of hybrid computers and show the application of an analog-parallel digital logic machine to two problems solved in our laboratory. The first concerns a program of data reduction leading to the thermodynamic characterization of the contractile state of the myocardium. The second problem relates to a theoretical analysis of the pressure-volume relationships in veins and thin walled tubes and incorporates a correlation of a computer simulation with actual experiments.

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50. A DIGITAL COMPUTER SYSTEM FOR CARDIOVASCULAR DATA ANALYSIS[1]

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Previous papers in this Symposium have described in some detail the methods and techniques available for obtaining cardiovascular data from a variety of animal preparations. The development of digital computer systems and the associated data processing techniques have given the investigator a powerful tool well adapted for analyzing large volumes of data rapidly and accurately. This paper will present, as an example of the numerous techniques available, a digital computer system and a program which have been used in our laboratory at Duke University Medical Center for the past two years to analyze hemodynamic data obtained from awake dogs chronically instrumented with electromagnetic flowmeter probes. It will serve to illustrate the use of a digital computer system for the reduction and analysis of cardiovascular data.

Figure 1 is a block diagram of the computer system currently in use. A Hewlett-Packard model 3520B analog tape playback unit with four parallel outputs is used to reproduce the data. A Sanborn model 760 eight-channel oscilloscope and a Sanborn model 358-100A eight-channel oscillograph are used to view the data as it is reproduced from the analog tape. The analysis system consists of a Redcor model 663 analog-to-digital converter directly coupled to an IBM 1130 computer system. The central processing unit of this system operates on a 3.6 microsecond memory cycle using 16-bit words. The core storage capability is 16K words and a 500K single-disk drive is used for off-line program and data storage. A Simulator model 240 analog computer is also available for signal pre-processing but is not used in the procedure to be described.

A computer system can acquire its data in two different environments; either on-line, where the recording equipment monitoring the experimental

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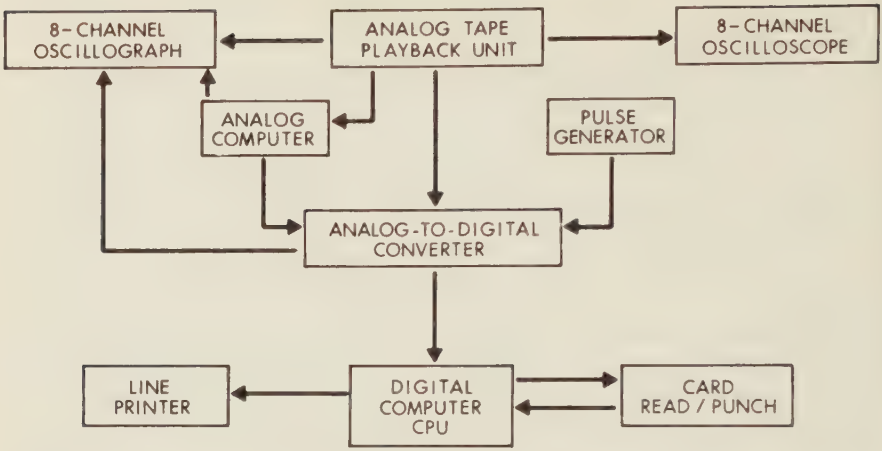

Fig. 1. Block diagram of a digital computer system for processing cardiovascular data.

preparation is fed directly to the computer system, or off-line, where the data is recorded on analog tape and processed through the computer at a later time. On-line analysis can be useful in situations where continuous monitoring of derived variables is required. However, most experimental protocols do not need this kind of rapid analysis and off-line methods are adequate and, in our opinion, preferred.

During the actual animal study our efforts are directed toward obtaining a good physiologic experiment and producing an analog tape record, using an eight-channel oscillograph to monitor the tape input continously. This tape is then processed at a later time and only those portions of the study which are of interest need to be analyzed.

The data for this sample analysis are obtained from awake dogs which have been surgically prepared at least two weeks prior to study. Aortic and left circumflex coronary artery blood flows are obtained from electromagnetic flowmeter probes, and aortic blood pressure is recorded through an indwelling polyvinyl chloride catheter. A mechanical snare is placed distal to the flow probe on the coronary vessel. The zero baseline for coronary artery blood flow is established at numerous times throughout the study by briefly occluding the snare. It is assumed that ascending aortic blood flow is zero during late diastole. Calibration signals from the flowmeters and pressure transducer, representing known amounts of flow and pressure, are recorded on the tape at the completion of the study and the digital computer is calibrated with these signals.

Data are sampled by the analog-to-digital converter at a rate controlled by the pulse generator and fed into the digital computer. A marker pulse is generated by the analog-to-digital converter whenever actual data conversion is taking place. This marker pulse is recorded on the oscillograph along with the raw data to produce a hard-copy record of the actual data as entered into the digital computer. The analog computer output can also be recorded on the oscillograph. In this way, data containing artifacts or that is unacceptable for any reason can be rejected before any further processing takes place. Figure 2 shows the record which was produced as the aortic blood pressure and the aortic and left circumflex blood flows were being sampled at 200/sec. These data are stored in individual 1000-point vectors in the computer. Note that the marker pulse from the analog-to-digital converter clearly indicates exactly which beats will be used for the subsequent analysis. This input run was considered acceptable and further processing was initiated.

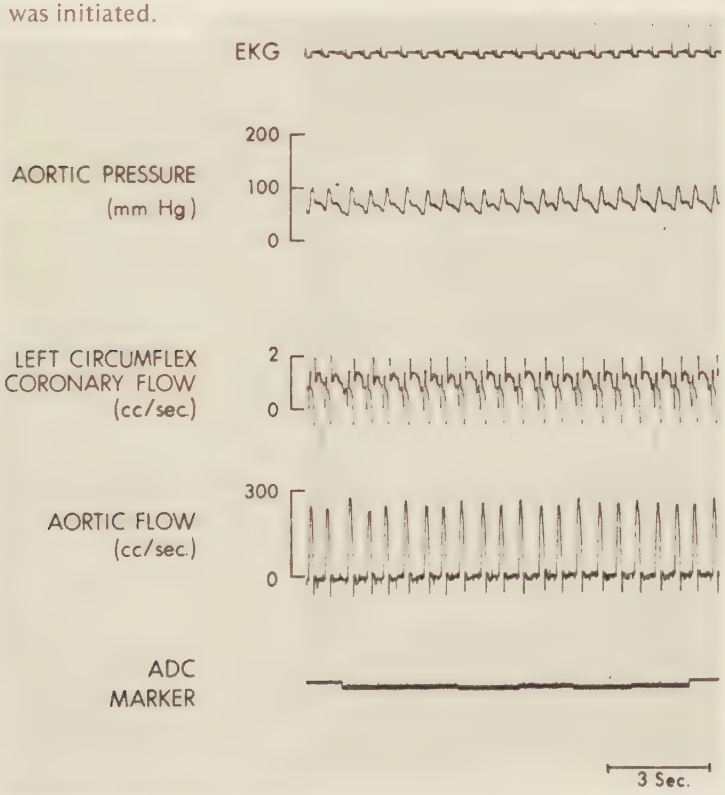

Fig. 2. Hard-copy record produced as data are processed by the analog-to-digital converter (ADC).

The actual data analysis is carried out on a beat-to-beat basis. To accomplish this, the beginning and end of each cardiac cycle must be identified, and the aortic blood flow data vector is used for this purpose. Assuming that this flow is essentially zero during diastole, the flow baseline can be checked and adjusted if necessary, using an algorithm developed for this purpose (1). Since systole is shorter than diastole, the most frequently occurring value in a sequence of digitized flow values will correspond to zero aortic flow. The digitized flow values are considered to be samples from a probability distribution with mode Θ and the baseline is determined by estimating Θ. This estimated value can be subtracted from all aortic flow data points to correct the baseline.

Each cardiac cycle is identified by three index points representing the end of ejection of the preceding beat and the beginning and end of ejection of the beat under consideration. Several methods are available for defining these points. The most direct method is to display the actual data vector on a suitable output device, manually identify the required index points, and enter these back into the computer. An automatic digital thresholding technique has also been used with some success, particularly when the aortic flow data contain no pacing artifacts or other noise spikes which cause false triggering. Another automated technique has been developed which can be used when pacing artifacts are present (1).

The next processing step is to display the actual data values for the first beat. This is shown in Figure 3. The first block of figures under each heading represent, reading left to right, the diastolic data values at each 5 msec interval. The second block of figures under each heading are the systolic data points. This output provides another visual check of the data as it is being processed.

Figure 4 shows the final output obtained from this program for the raw data presented previously. The data column headings represent, reading left to right, the R-R interval (sec), estimated as the total length of the cardiac cycle, duration of ejection and duration of diastole (sec), stroke volume (cm^3), peak flow rate (cm^3/sec), left circumflex coronary stroke diastolic and systolic blood flows (cm^3), systolic, diastolic, and mean aortic pressure (mmHg), tension-time index (mmHg-sec/min), peak power (gm-cm/sec), and stroke work (gm-cm). This printout indicates that a total of 16 beats were found and these final data for each beat are punched on cards, one beat per card. The mean and standard error of each column is determined and the data is then summarized. This printout allows further inspection of the data for analysis errors. By direct comparison of this output with the hard-copy record produced when the data entered the computer, any beat values which are obviously in error can be identified. The card representing this

CONTROL DOG 11 DATE OF STUDY = 10/13/69 ISAM = 200

AORTIC FLOW DATA

-47.975	-65.308	-58.498	-36.832	-23.832	-3.404	14.547	9.595	12.071	7.737
0.928	2.166	-0.309	-4.642	-5.261	-7.118	-9.595	-11.452	-11.452	-12.690
-21.356	-20.118	-22.594	-25.689	-22.594	-19.499	-20.737	-20.118	-13.928	-9.595
-12.690	-8.356	-2.785	-5.880	-10.833	-0.309	12.071	8.356	0.309	-7.737
-12.690	-9.595	-1.547	-8.356	-4.642	-7.118	-4.642	-0.928	4.023	5.880
4.023	0.928	2.166	-1.547	-2.166	-1.547	2.166	-8.356	-7.737	0.309
-4.642	-5.261	-4.023	-4.642	-3.404	-1.547	0.309	-6.499	-15.166	-18.261
-13.309	-15.166	-8.356	-13.928	-8.356	-9.595	-2.166	-2.166	-5.880	6.499
6.499	18.261	36.213	60.974	98.736	127.211	160.639	176.115	194.686	208.305
225.638	230.590	227.495	241.113	241.113	230.780	239.256	239.256	228.114	221.304
211.400	199.019	189.115	176.714	165.591	151.353	131.544	109.259	82.641	54.165
20.118	-13.928								

CORONARY FLOW DATA

-0.815	-0.337	0.426	1.179	1.752	2.122	2.146	1.979	1.752	1.430
1.155	1.012	0.976	1.036	1.119	1.274	1.418	1.477	1.501	1.537
1.466	1.549	1.537	1.489	1.466	1.513	1.454	1.489	1.477	1.454
1.370	1.346	1.394	1.346	1.298	1.274	1.346	1.370	1.322	1.394
1.346	1.370	1.382	1.310	1.334	1.274	1.274	1.239	1.262	1.262
1.143	1.191	1.203	1.119	1.000	0.976	0.940	0.856	0.713	0.773
0.761	0.737	0.844	0.833	0.821	0.880	0.928	0.928	0.916	0.916
0.928	0.904	0.809	0.594	0.438	0.283	0.128	0.020	-0.182	-0.086
-0.086	0.080	0.403	0.761	1.155	1.310	1.454	1.513	1.430	1.251
1.107	0.952	0.749	0.713	0.665	0.665	0.653	0.737	0.689	0.653
0.630	0.558	0.546	0.510	0.474	0.426	0.331	0.200	0.056	-0.146
-0.373	-0.659								

AORTIC PRESSURE DATA

76.215	74.047	71.880	74.589	74.589	77.299	78.383	74.047	73.505	71.338
67.544	72.964	67.544	67.544	70.254	69.170	67.002	69.712	68.628	67.002
64.292	69.712	68.628	67.544	68.628	72.964	70.254	66.460	68.628	71.338
69.712	73.505	73.505	71.880	68.086	65.918	68.086	68.628	67.002	65.918
65.376	67.002	68.628	65.918	62.124	62.124	66.460	61.582	66.460	70.254
67.002	63.750	66.460	64.292	63.208	64.834	70.254	61.040	59.956	63.208
59.414	59.956	61.040	58.330	61.582	58.330	54.536	51.826	57.246	53.452
57.246	50.742	54.536	48.032	48.032	47.490	56.162	53.994	49.116	52.910
52.910	56.704	58.872	56.704	62.666	62.124	72.964	72.422	75.131	75.673
81.093	84.887	80.009	89.223	94.643	92.475	91.391	96.269	94.643	96.811
96.811	97.895	96.811	94.643	95.727	97.353	93.017	91.391	91.391	84.345
86.513	86.513								

Fig. 3. Raw data at 5 msec intervals for the first beat identified.

CONTROL DOG 11 DATE OF STUDY = 10/13/69 ISAM = 200

	RRINT	DE	DD	SV	PKFLQ	CDF	CSF	S-AOP	D-AOP	M-AOP	TTI	PKPWR	SW
1	0.550	0.155	0.395	24.49	241.11	0.441	0.098	97.89	47.49	70.30	1412.90	31329.	2904.1
2	0.509	0.170	0.340	27.73	264.01	0.365	0.101	103.85	52.36	72.46	1720.54	35710.	3473.1
3	0.615	0.185	0.430	31.19	281.97	0.465	0.112	106.56	50.20	70.91	1533.03	39103.	3901.3
4	0.620	0.185	0.435	27.93	262.78	0.500	0.109	101.68	48.57	68.88	1439.77	33441.	3340.2
5	0.509	0.185	0.325	26.75	259.06	0.375	0.101	998.12	57.24	81.10	2077.25	34305.	3326.5
6	0.560	0.180	0.379	30.45	280.73	0.420	0.110	108.19	51.82	72.40	1668.18	38004.	3845.2
7	0.655	0.185	0.470	29.47	270.20	0.535	0.108	101.14	46.40	69.10	1380.71	35765.	3543.6
8	0.545	0.180	0.365	27.33	265.25	0.419	0.102	102.77	55.62	72.64	1674.11	36103.	3372.1
9	0.610	0.185	0.425	31.60	281.97	0.467	0.115	106.56	48.57	73.29	1582.65	38416.	4029.5
10	0.615	0.189	0.425	27.93	262.78	0.494	0.103	99.52	49.65	71.42	1481.78	33461.	3340.8
11	0.530	0.189	0.340	27.87	264.01	0.403	0.112	105.48	55.62	73.85	1819.51	35545.	3498.4
12	0.605	0.200	0.405	32.57	288.77	0.453	0.120	112.52	49.65	74.59	1719.99	41141.	4193.6
13	0.629	0.189	0.439	29.03	270.20	0.509	0.108	108.19	48.57	72.61	1694.18	34785.	3585.1
14	0.565	0.189	0.375	28.63	265.25	0.434	0.099	106.56	53.99	72.23	1596.08	35874.	3531.6
15	0.570	0.210	0.360	31.10	280.11	0.422	0.126	109.27	53.45	75.08	1846.23	40190.	4011.2
16	0.615	0.180	0.435	29.26	273.30	0.494	0.110	107.10	51.28	72.54	1693.48	36461.	3669.8
MEAN	0.581	0.184	0.396	28.96	269.47	0.450	0.108	160.96	51.28	72.71	1628.09	36227.	3597.93
STANDARD ERROR	0.011	0.002	0.010	0.51	2.91	0.012	0.001	55.81	0.79	0.70	47.18	653.	82.71

HR = 103.1 BEATS/MIN MEAN AORTIC PRESSURE = 72.7 MM-HG

SYSTEMIC FLOW

STROKE VOLUME = 28.9 CC
DURATION OF EJECTION = 0.184 SEC
PEAK FLOW = 269.4 CC/SEC
STROKE WORK = 3597.93 GM-CM
TENSION-TIME INDEX = 1628.09 (MM-HG*SEC)/MIN

CARDIAC OUTPUT = 2988.9 CC/MIN
MEAN EJECTION RATE = 156.5 CC/SEC
PVR = 1945.8 DYNE-SEC/CM**5
PEAK POWER = 36227. GM-CM/SEC

CORONARY FLOW

DIASTOLIC	SYSTOLIC	TOTAL	
0.450	0.108	0.559	CC/BEAT
46.4	11.2	57.6	CC/MIN

CVR = 100806.5 DYNE-SEC/CM**5

Fig. 4. Final data output produced by the system described in the text.

beat can be removed from the output deck and an option is provided to regenerate the entire last output page, using the previously punched cards as input. If an automated beat identification procedure is used, the total time required by this program from data entry to the punching of the output deck is approximately five minutes.

This program system provides an example of an efficient method of analyzing hemodynamic data from awake dogs. The most important features are the numerous data checking steps which are an integral part of the processing. Checks like these must be built into any data processing system to minimize the possibility of producing erroneous results based on faulty input data.

SUMMARY

A digital computer system and an analysis program have been presented as an example of the numerous techniques available for processing cardiovascular data. The specific program presented is used to analyze left circumflex coronary artery and aortic blood flow data obtained from chronically instrumented dogs on a beat-to-beat basis. Particular attention has been given to a description of the data checking steps necessary to minimize processing errors.

ADDENDUM

Another automated technique for identifying the onset and end of ventricular ejection, which uses the pulsatile central aortic blood pressure and the electrocardiogram, has been developed recently (2). The R-wave of the electrocardiogram is used to identify a segment of the aortic pressure which has a high probability of containing the beginning of ejection. The onset of ejection is defined as that point in the pressure wave which is followed by four consecutive first derivatives greater than 10 mm Hg/sec and which occur between 30 and 200 msec after the R-wave of the electrocardiogram. The dicrotic notch is located by searching the aortic pressure data for the maximum second derivative which occurs between 30 msec after the peak systolic pressure point and 300 msec after the onset of ejection. The reliability of this new technique was evaluated by comparing the index points found by the pressure method to those obtained by the algorithm which uses aortic flow (2), and excellent correlations were obtained.

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51. A USER-INTERACTIVE DATA ACQUISITION AND REDUCTION SYSTEM FOR THE STUDY OF CARDIAC DYNAMICS

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INTRODUCTION

A major aim of our research group is developing techniques and instrumentation for the long-term study of cardiac dynamics in conscious dogs, and determining the hierarchy of neuro-humoral factors modulating left ventricular performance. The large quantity of data generated continuously by the several implanted transducers during the course of an experiment, and the extensive calculations required to reduce and aggregate the data to a form suitable for interpretation have prompted the development of an automatic data acquisition and reduction system in our laboratory.

Generally, the system design objectives are to provide the cardiovascular physiologist with the capability of:

(1) on-line digitizing of several channels of analog data at prescribed periods of time and sampling rates, upon instruction of the investigator;

(2) filing and retrieving large amounts of data from a particular experiment or group of experiments for subsequent off-line reduction and analysis;

(3) monitoring the course of an experiment by having the option of on-line display and printout of data as a basis for decisions regarding the progress of an experiment; and

(4) providing simple and flexible off-line manipulation and summarization of data in the form of derived physical variables, statistical summaries of measured and derived variables, and graphic displays (cross-plots, histograms, cross-correlations, etc.) of chosen variables.

Although many features incorporated in the system are peculiar to measurements readily available from chronic animals in our laboratory, it is sufficiently flexible for application in clinical and other types of cardiovascular studies. In many respects the system is similar to others described in the literature (1-7), yet it has uniqueness in the number of options available to the investigator, in some of the programming algorithms for analyzing events in the heart cycle, and in its application to awake, instrumented animals.

The purpose of this report is to describe the hardware system for retrieving and processing measured variables, the overall software design for implementing the system objectives, and the programming methods for signal pattern recognition and for calculation of derived variables.

SYSTEM HARDWARE

Transducers for measuring variables

Various combinations of transducers are implanted in the animal depending on the objective and length of the experiment. Figure 1 shows diagrammatically the location of several types of sensors that we usually have implanted surgically in dogs. These include pressure cells for measuring left ventricular, aortic, and atrial pressures, and electromagnetic coils for measuring internal and external equatorial diameters. (Externally excited primary coils induce a voltage in diametrically opposite secondary coils. The magnitude of the induced signal varies inversely with the distance between coils; special instrumentation developed by the members of the research team linearizes the relationship between coil separation and the ultimate signal [8]). External electrodes are used for obtaining an electrocardiogram. Sometimes, an electromagnetic flow probe is implanted over a Dacron sleeve, on the ascending aorta. Metal markers are placed subendocardially for biplane cineradiographic estimation of instantaneous volume. Both of these latter methods serve as a basis for validating flow and volume estimations which we derive directly from ventricular diameter measurements.

Signal Distribution

The electrical output from all these implanted sensing devices and the ECG electrodes are cabled to appropriate carrier, DC coupling, and high and low gain amplifiers shown schematically in Figure 2. Amplified and conditioned signals are then distributed, as required, by patch panel con-

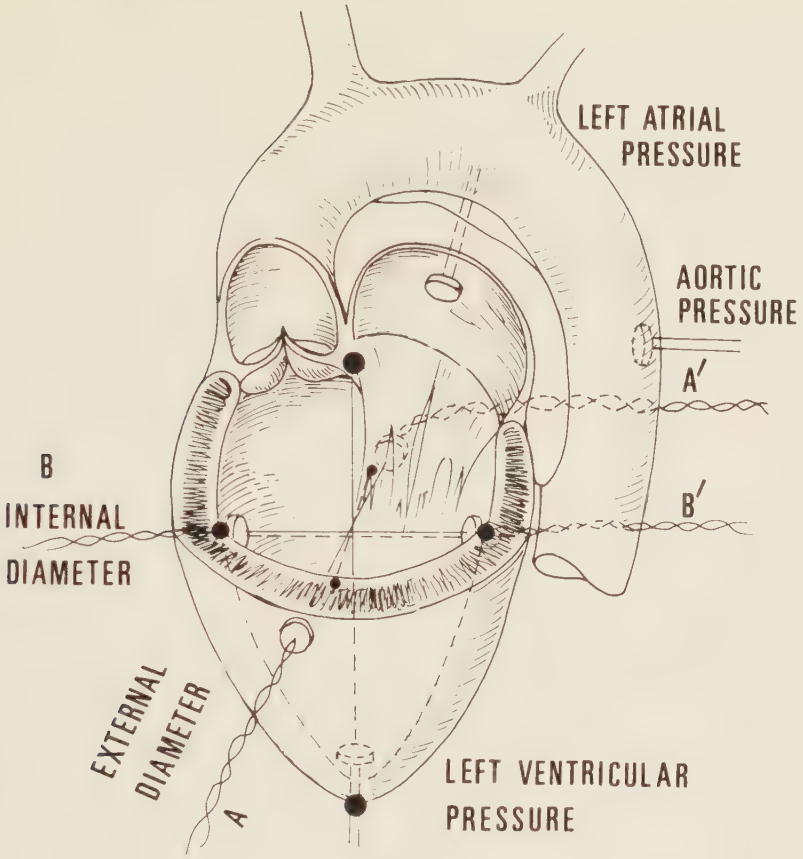

Fig. 1. Location of sensors.

nections to: recording system for permanent graphic charts of waveforms; multi-channel seventeen-inch oscilloscope (CRO) for waveform display; analog magnetic tape records for storage of all data signals; analog computer for continuous processing; and an analog-to-digital converter, for input to the computer instrumentation. Experimental data can be sampled on-line, as well as replayed from magnetic tape for study and selection of portions for detailed analysis by the computer.

Computer Hardware

Our laboratory is currently equipped with a Hewlett-Packard 2116B digital computer with 16K words of main memory (16 bit words) and two

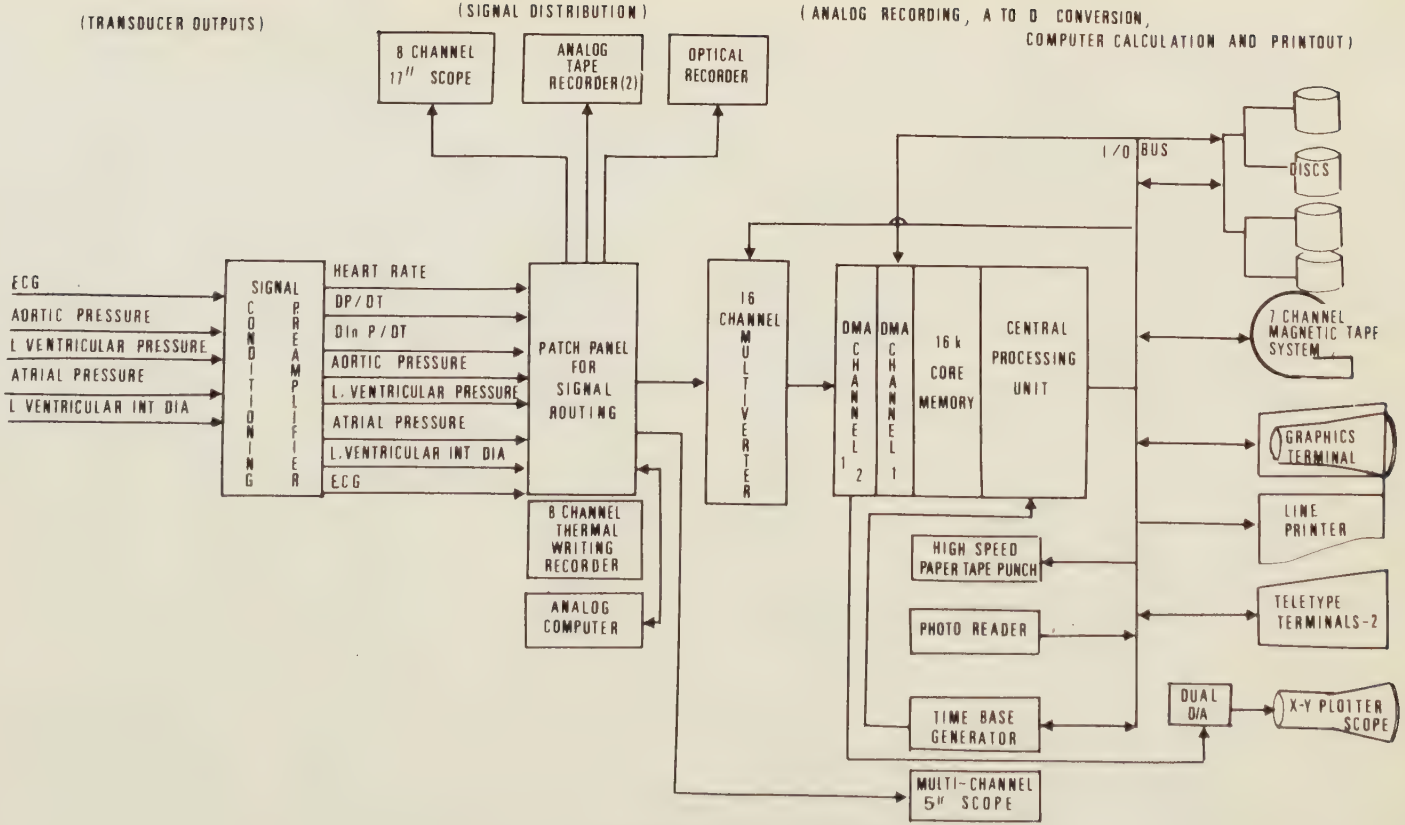

Fig. 2. Data acquisition and processing.

direct memory access channels allowing data transmission rates up to 625 KHz by interleaving channels (Fig. 2). Peripheral devices include a multiplexed 16 channel, 14 bit resolution analog to digital converter capable of through-put rates of 18 KHz; two moving head disc drives, each with a fixed disc and a removable cartridge providing a peripheral storage capability of 2.6 million words, accessible at a transfer rate of 45 KHz; a 7-channel magnetic tape unit (200 bits/in, 30 in/sec); a high speed printer (300 lines/min); two teletypes for keyboard input/output; and an X-Y plotter CRO.

Recently, a Tektronix 4002A graphic terminal (display matrix of 1024 x 760 points and transfer rate of 5000 characters/sec) has been added to the system to maximize real-time interactive capability between the investigator and the experiment, and to facilitate on-line editing and composing of programs and displays.

Presently, the hardware system is supervised by a HP DOSM operating system with special input/output routines to facilitate continuous sampling and storage of large blocks of data (up to 500,000 words). The DOSM operating system simplifies user program development, file management, and data processing, and is effective for those operations where the computer can be dedicated to a single activity. However, future plans call for the addition of a real-time multiprogramming system. For example, under a real time supervisory system the computer may be concurrently monitoring the clinical status of several animals while the investigator is conducting an experiment in the laboratory, and/or members of the research team are developing new programs or processing stored data.

PROGRAM DESIGN CONSIDERATIONS

The program design for an on-line interactive system depends very strongly on the hardware characteristics and the supervisory program managing the hardware and the execution of user programs. Regardless of the environment in which these programs are developed, they essentially consist of the six major components listed below, with pertinent factors in program design also noted.

1. Data acquisition (number of channels, rate of scanning) and storage (length of record, core memory size, peripheral memory size).
2. Pattern recognition.
3. Data reduction (calibration, choice of derived variables).
4. File organization and management.
5. Data analysis (single cycle or multiple cycle, transient or steady state, statistical aggregations or functional description).

6. Raw and processed data output (mode and format: CRO, printer, graphic terminal, etc.).

The accomplishment of these functions, viewed independently, remains relatively static as the system develops. However, the interrelationships of these tasks change dramatically with the status of the hardware and supervisory system environments. The kinds of changes that have taken place over the course of the development of our system are:

(1) the amount of uninterrupted data which can be stored and retrieved in either core or peripheral memory,

(2) the extent to which data can be analyzed while the experiment is in progress,

(3) the "quick look" at raw and reduced data as a basis for real-time modification of experimental procedures, and

(4) the simplicity and flexibility with which data can be retrieved from files, manipulated and edited by data analysis routines, and displayed or printed out for a more leisurely view by the investigator.

Figure 3 was prepared as a guide to the investigator planning an experiment and illustrates the factors which must be considered in determining the on-line interrelationships of the various components of the user programs. The word storage capacity required to hold data from a chosen number of heart cycles is shown as a function of the average heart rate. Labeled in the graph are the storage requirements for 5 and for 50 heart cycles at the same average heart rate of 150 beats/minute. In a system simply monitoring short bursts of uninterrupted data (the 5 cycle case), the information can be readily stored in core memory and processed and displayed on-line, whereas for the longer case (50 cycles), post-experiment, off-line processing of data would probably be more effective.

A configuration of program components recently used for monitoring short bursts of data (2 sec) and on-line reduction is illustrated in the logic flow diagram, Figs. 4 a, b, and c. A modular program, currently under development, allows retrieval of variable length records and greater flexibility in its interrelationship with other program components (Fig. 5).

The implementation of a real-time supervisory system will alter this interrelationship somewhat by allowing interleaving of processing display in the time intervals between scanning the data channels. In contrast to on-line processing under the present DOSM system, a real-time capability is achieved in the sense of virtually concurrent data retrieval, processing, and display.

The subsequent section of this report will be devoted to a description of the major components of the program design, with the understanding that details of this interaction are continually in a state of flux.

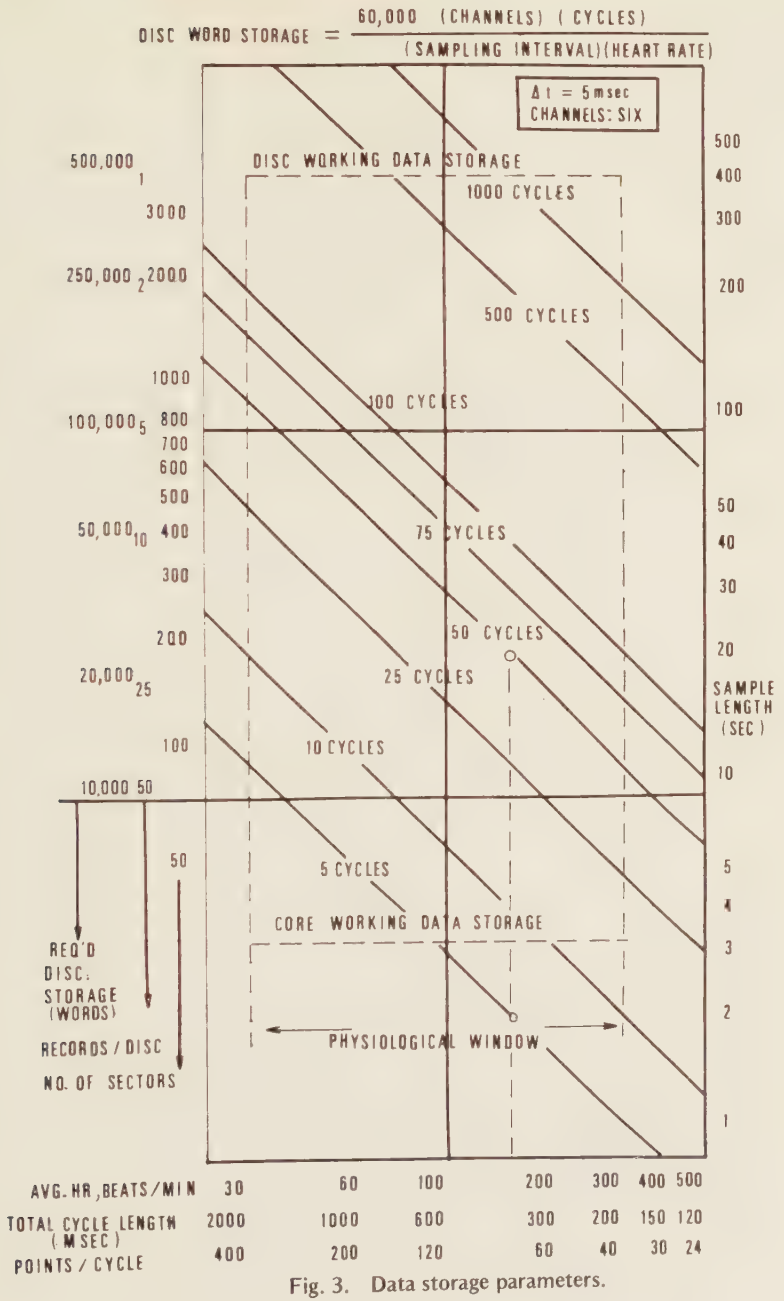

Fig. 3. Data storage parameters.

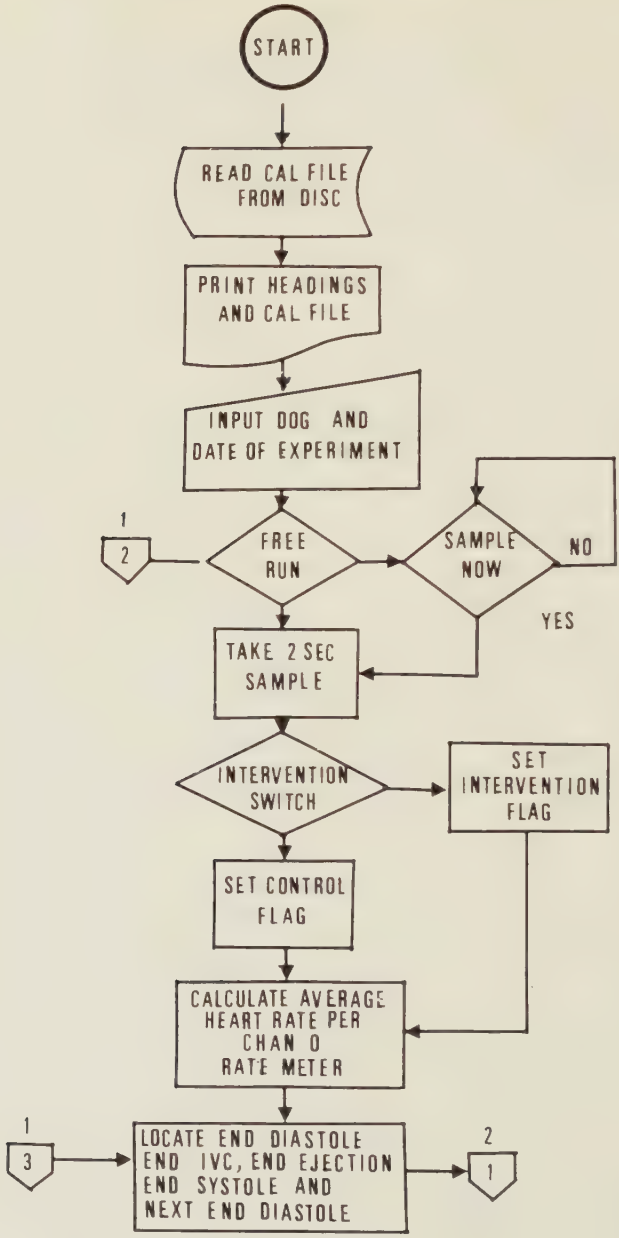

Fig. 4a. Data acquisition and on-line reduction.

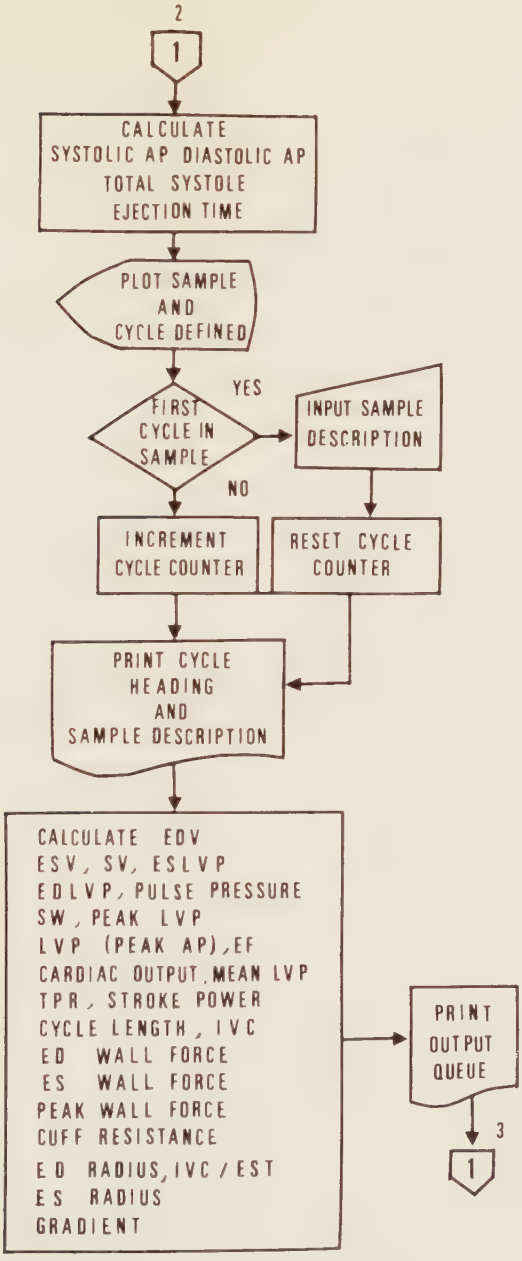

Fig. 4b. Data acquisition and on-line reduction.

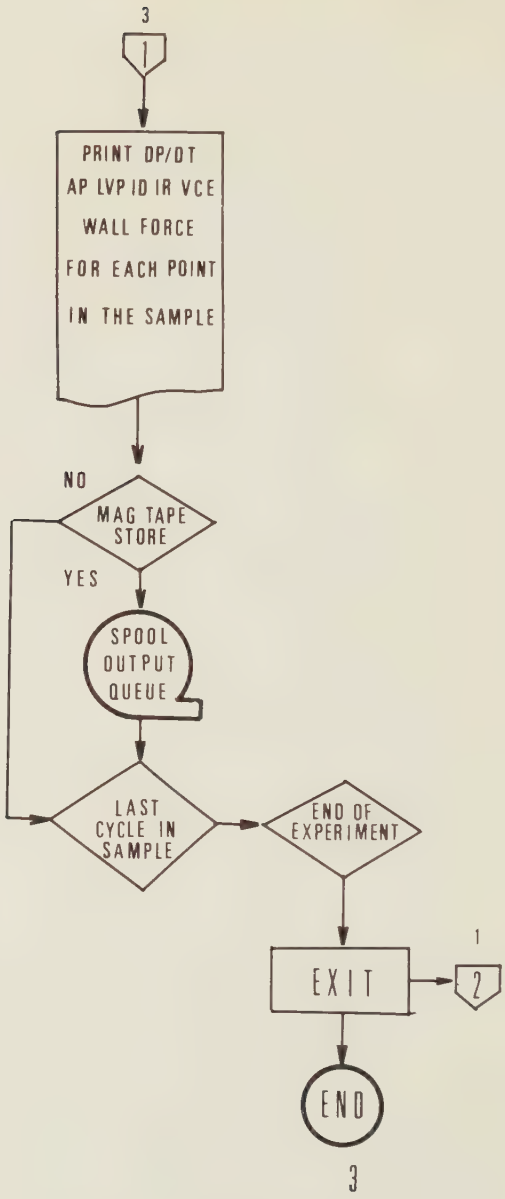

Fig. 4c. Data acquisition and on-line reduction.

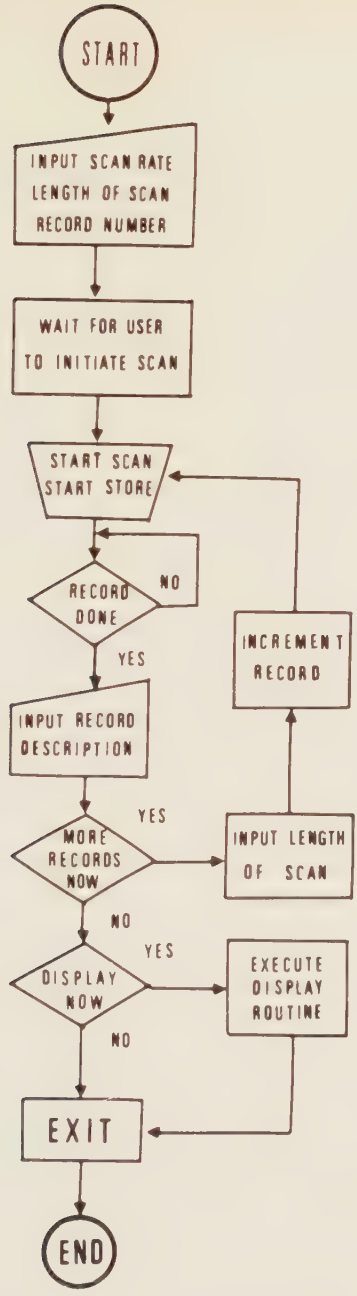

Fig. 5. Continous data acquisition.

DATA ACQUISITION AND STORAGE

Data acquisition is normally preceded by determination of the calibration constant for the variable digitized and either creating or updating a file for the animal being monitored. Calibration is initiated by assigning variables to selected channels. Currently seven channels are standard: heart rate, dP/dt, dLnP/dt, aortic pressure, left ventricular and left atrial pressures, and left ventricular internal diameter. Any of these seven variables may be replaced by different variables, and other variables may be assigned to the remaining 9 channels. The lower limit of the calibration values is entered on the keyboard, and sampling and storage of lower standard voltages corresponding to the lower calibration values is initiated by operator depression of a code number on the keyboard. Similarly, high calibration values and standard voltages are entered and the computer then calculates and displays the appropriate factors for calibrating the measured variable for the investigator's review. After creating or updating a file for the animal being studied, the operator must enter the time interval between samples and the length of the record. Up to sixteen channels may be scanned sequentially at prescribed time intervals and scan rates from 1 msec to 5 msec, and records of up to ½ million words of uninterrupted data may be stored in a file on the subchannel of the discs.

The sampling process is initiated through a control box operated by the physiologist. The control also activates a marker on the strip chart recording, enabling the investigator to correlate analog and digitized data.

Presently under separate programs, the investigator has the option of on-line processing where either automatically or upon command the computer samples bursts of data over short time intervals and then displays and/or prints out information between successive samplings, or alternately, when long records are required, the data may be continuously transferred to the disc for subsequent off-line processing. When long records are written on the disc, a description of the record is entered on the terminal following the sampling of data to allow investigator notation of any unusual observations from the analog strip chart recording or reactions of the animal.

When the graphic terminal is fully integrated into the system, these options may be executed under the control of a single program and terminal as illustrated in the flow diagram of Figure 6. Also illustrated in this figure is the proposed organization of file information and the format for automatically addressing inquiries to the investigator in creating or updating files using the graphics terminal.

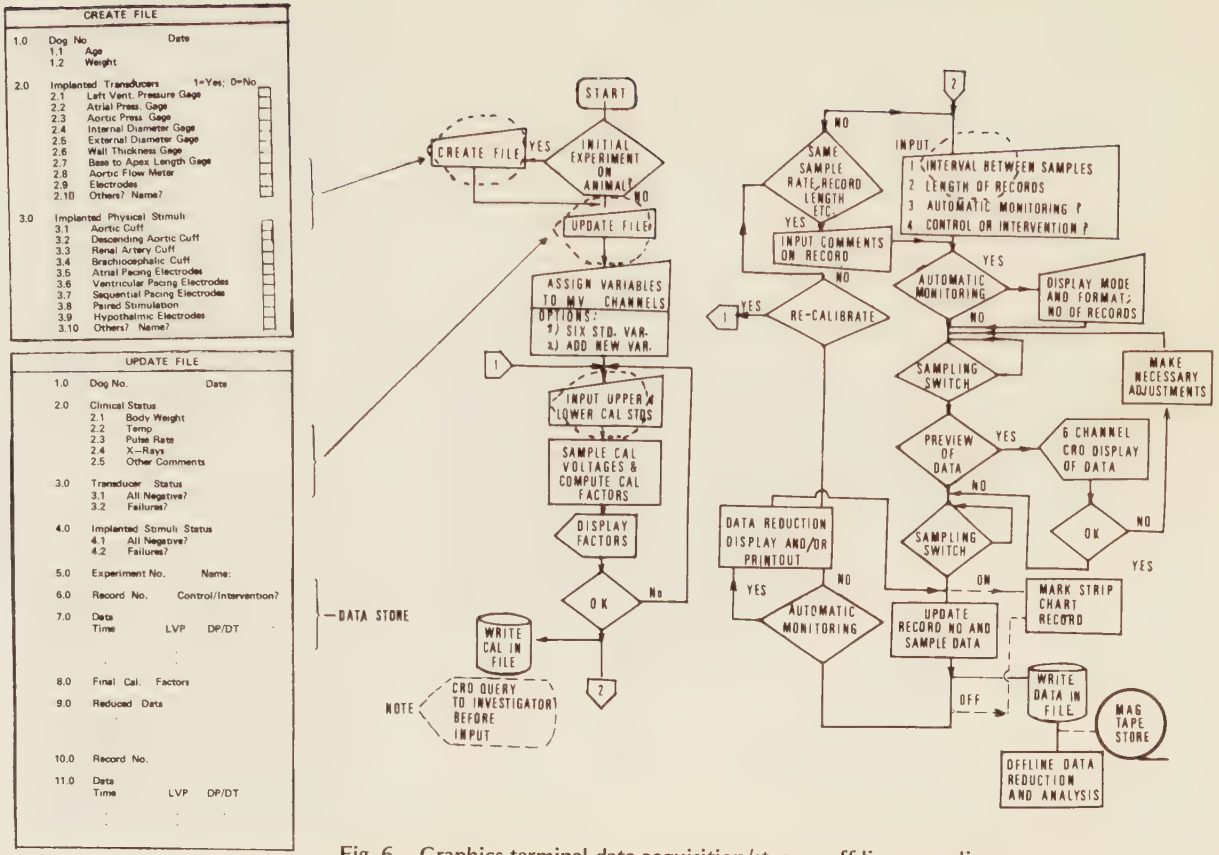

Fig. 6. Graphics terminal data acquisition/storage off-line or on-line.

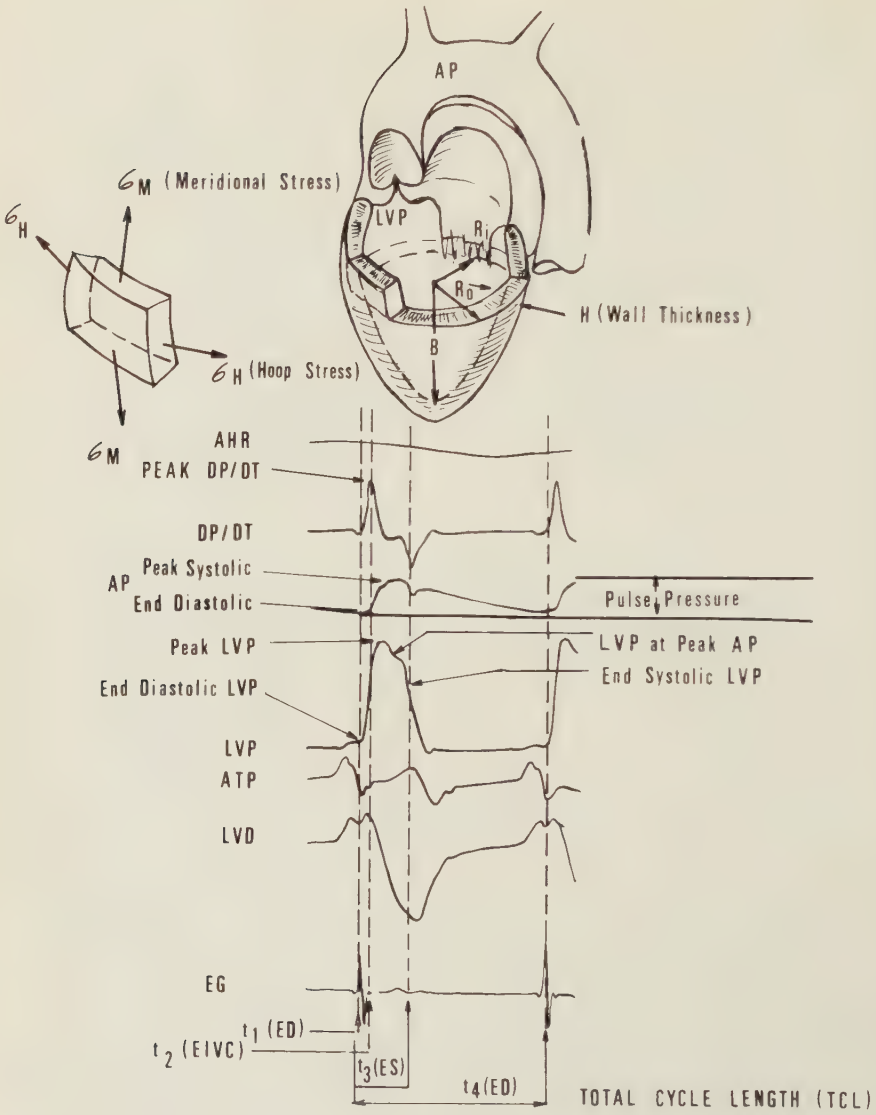

Fig. 7. Cardiac cycle definition.

CARDIAC CYCLE RECOGNITION

All phases of the heart cycle and the other characteristics indicated in the strip chart recording of Figure 7 are automatically identified and labeled sequentially for each heart cycle in the digitized record of a sample. One mode of displaying a heart cycle and its phases uses the CRO as illustrated in Figure 8. The vertical lines marking end-diastole (ED1), end-isovolumic contraction (EIVC), end-ejection (EE), and the end-diastole of the succeeding beat (ED2) have been automatically defined by the computer. In addition to defining critical events of each cardiac cycle, these labels serve as a pointer for subsequently determining derived variables.

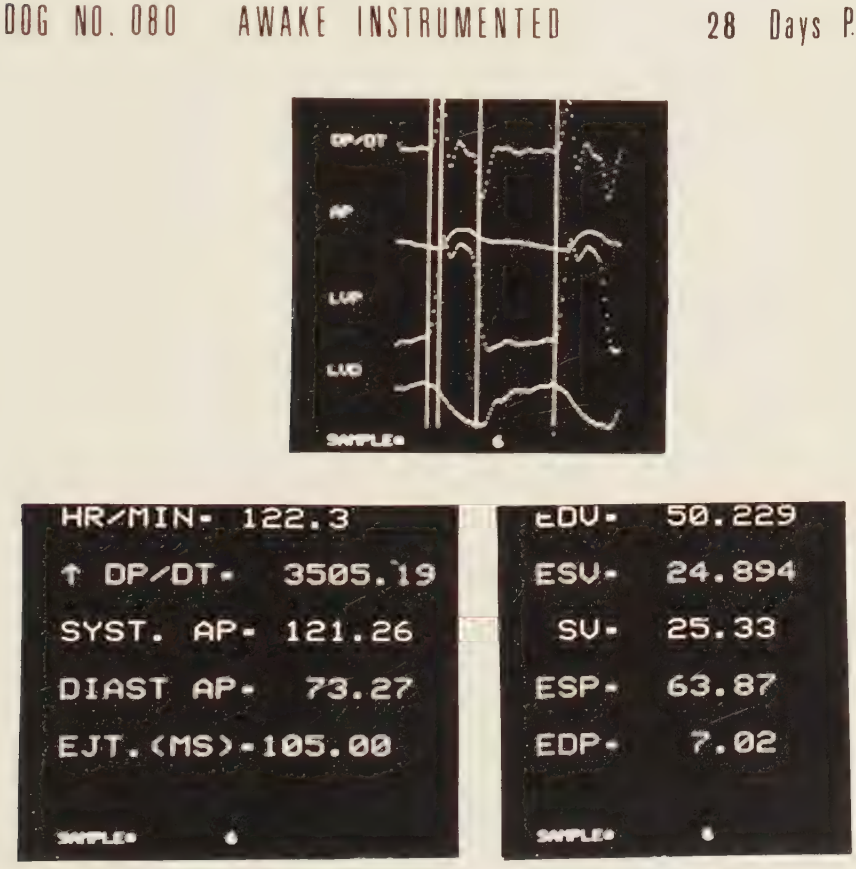

Fig. 8. CRO display.

As the computer proceeds serially through the digitized cycle, it sequentially numbers the cycles, starting with the first analyzed, enabling the investigator to correlate the digitized computer record with the analog strip chart record.

Presently, the key measured variables in the cardiac cycle definition algorithm are the plus and minus peak values of dP/dt. These values define neighborhoods in which to search for other critical events and serve as pointers themselves for *end-isovolumic contraction* and *end-ejection.*

As demonstrated in several studies concerned with evaluating myocardial contractility (9, 10), we have found that except in the case of high afterloads (the limiting case being isovolumic contraction), peak positive dP/dt occurs at approximately the beginning of ejection minus an empirical number of time intervals. Again, except in the case of high afterloads, peak negative dP/dt occurs at approximately end-ejection minus an empirical number of time intervals (approximately 20 msec). Thus when aortic pressure is measured, the times of occurrence of these peaks defines neighborhoods for searching for minimum or discontinuous changes in slope, respectively, of the aortic pressure curve as indices of beginning of ejection and end-ejection. Fortunately, the low distortion of the transducer-amplifier system and the fact that in chronic animals the aortic pressure may be measured proximal to the aortic valve has relieved the problem of time delay between the aortic and ventricular pressure signals frequently occurring in clinical studies (3).

Basically, the computer starts at the beginning of a record by comparing values of peak dP/dt until a local maximum above a prescribed threshold value is found. The search is restricted approximately to a time window of the record corresponding to the minimum cycle length that is likely to be found. The threshold level, 600 mm Hg/sec, was empirically determined as a means of discriminating between true peak dP/dt and artifacts occurring in the ventricular pressure curve during diastole. If after searching through a series of time windows, approximating the longest cycle apt to occur, both peaks are not disclosed for some reason, a message "warning: peak dP/dt unrecognizable" is sent to the investigator and the search continues through another series of windows until peaks are located for the next cycle.

The 5 msec intervals between scanning all selected channels yields a maximum error in determining the time of the peak dP/dt's of ± 2.5 msec and a maximum error in the value of the peak dP/dt's of approximately 5%. When increased accuracy is required, the investigator has the option of reducing the time between samples down to 1 msec or introducing extrapolation algorithms into the program. This latter time interval is the most desirable and should be used whenever possible.

End-diastole is found by searching backward in time from peak positive dP/dt until a minimum value of dP/dt is found. In the absence of a distinct atrial kick in the ventricular pressure curve, the minimum valve occurs earlier in the heart cycle than the time which cardiologists would denote as end-diastole. Consequently, the location is validated by requiring that the succeeding value of left ventricular pressure be at least 4 mm Hg higher than the minimum pressure. If this condition is not satisfied, the left ventricular pressure curve is searched forward in time from this point until this condition is satisfied, and then this time is denoted as *end-diastole.*

- HEART GEOMETRY

  Wall thickness
  $H = R_o - R_i$

  Axis ratio
  $\alpha = B/R_i$

  Volume
  $V = 4/3\ \Pi\ \alpha\ R_i^3$

  Stroke volume
  $SV = EDV - ESV$

  Ejection fraction
  $EF = 1 - ESV/EDV$

  Cardiac output
  $CO = SV * Hr/1000$ or
  $60 * SV/TCL$

- WALL FORCE AND STRESS

  Wall force
  $WF = 1.36 * LVP * \Pi\ R_i^2$

  Meridional stress
  $$\sigma m = \frac{1.36 * LVP * R_i^2}{R_o^2 - R_i^2}$$ or
  $$\frac{1.36 * LVP * R_i}{2H\ (1 + H/2R_i)}$$

  Circumferential stress
  $$\sigma h = \frac{1.36 * LVP * R_i}{H} \left[\frac{1}{1 + H/2R_i \alpha 2}\right]\left[1 - .5/\alpha 2\right]$$

- PRESSURE QUANTITIES

  Grad. = Peak systolic AP minus LVP at peak systolic AP

  PP = Peak AP minus end diastolic AP

  Mean aortic pressure
  $$MAP = \frac{1}{TCL}\int_{t_1}^{t_4} (AP)\ dt = \sum_{i=1}^{N} \frac{(AP)_i}{N}$$

- CONTRACTION VELOCITIES AT EQUATOR

  Circumferential fiber
  $$VCF\ (t) = 2\ \Pi \left[\frac{R_m\ (t + \Delta t\ -\ R_m\ (t - \Delta t)}{2 \Delta t\ L_o}\right]$$

  Series elastic
  $$VSE\ (t) = \frac{d\sigma h}{dt} \Big/ 34\ (\sigma_h + 19)$$

  Contractile element
  $VCE\ (t) = VCF\ (t) - VCE\ (t)$
  or during IVC,
  $$VCE = \frac{1}{34}\ \frac{d\ Ln}{dt}\ (Ln P)$$

- ENERGY QUANTITIES

  Stroke work
  $$SW = -1.36 \times 10^{-2} \int_{t_2}^{t_3} (LVP)\ dV$$
  $$= -1.36 \times 10^{-2} \sum_{i=1}^{N} \frac{P_i + P_i + 1}{2} (V_i - V_i + 1)$$

  Stroke power
  $SP = SW/(1000 * EJT)$

- RESISTANCE

  Total peripheral resistance
  $$TPR = 79.68 \left[\frac{MAP\ -\ EDP}{CO}\right]$$

- PHASE LENGTHS

  Total cycle length
  $TCL = t_4\ (ED) - t_1\ (ED)$

  Period of isovolumic contraction
  $TIVC = t_2\ (EIVC) - t_1\ (ED)$

  Ejection time
  $EJT = t_3\ (ES) - t_2\ (EIVC)$

Fig. 9. Left ventricular derived variables.

Table 1

Abbreviations and Units of Measurement for Measured and Derived Variables

ABBREVIATION	VARIABLE	UNITS
a	Ratio of aorta to apex length to inside radius at equator	dimensionless
σ_h	Hoop stress	GM/CM^2
σ_m	Meridional stress	GM/CM^2
AP	Aortic pressure	mmHg
B	One-half aorta to apex length	CM
CO	Cardiac output	L/min
EDV	End diastolic volume	CM^3
EF	Ejection fraction	dimensionless
EJT	Ejection time	MSEC
EDP	End diastolic pressure	mmHg
ESV	End systolic volume	CM^3
GRAD	Pressure gradient	mmHg
H	Wall thickness at equator	CM
HR	Heart rate	beats/min
Lo	Reference circumference	CM
LVP	Left ventricular pressure	mmHg
MAP	Mean aortic pressure	mmHg
PP	Pulse pressure	mmHg
R_i	Inside radius at equator	CM
R_m	Mean radius at equator	CM
R_o	External radius at equator	CM
SP	Stroke power	GM-meters/sec
SV	Stroke volume	CM^3
SW	Stroke work	GM-meters
t_1, t_2, t_3, t_4	Time at end diastole (ED), end isovolumic contraction (EIVC), end systole (ES), and end diastole of following cycle, respectively	msec
TCL	Total cycle length	msec
TIVC	Period of isovolumic contraction	msec
TPR	Total peripheral resistance	$dynes\text{-}sec/CM^5$
t	Time of measurement	msec
V	Volume	CM^3
WF	Wall force	grams
VCF, VSE, VCE	Contractile fiber, series elastic, and contractile element velocities, respectively	muscle lengths/sec

Once these times have been established, it is a simple matter to determine quantities such as beat period, peak LVP, peak AP, etc. for the particular cycle and for the successive cycles on the digitized record.

REDUCTION OF DATA-DERIVED VARIABLES

Once the phases of the heart cycle have been found, the family of derived variables used by cardiologists and experimental physiologists to assess left ventricular performance may be calculated for each heart cycle (Fig. 9, Table 1). An example of the computer printout of some of these variables is shown in table 2, and a corresponding oscilloscope display is shown in Figure 8.

TABLE 2

THE TYPICAL PRINTOUT FROM A SINGLE CARDIAC CYCLE

DOG # 80 SAMPLE # 5 DATE 7/28/70

AVERAGE HEART RATE/MIN	=	214	
PEAK DP/DT	=	6978	MM HG/SEC
PEAK SYSTOLIC AP	=	142	MM HG
DIASTOLIC AP	=	110	MM HG
MEAN AORTIC PRESSURE	=	123	MM HG
PULSE PRESSURE	=	32	MM HG
END DIASTOLIC VOLUME	=	73.5	CC
END SYSTOLIC VOLUME	=	56.7	CC
STROKE VOLUME	=	16.7	CC
EJECTION FRACTION	=	23	%
CARDIAC OUTPUT	=	3.6	L/MIN
END DIASTOLIC LVP	=	2.7	MM HG
LVP AT PEAK AP	=	132	MM HG
END SYSTOLIC LVP	=	55	MM HG
STROKE WORK	=	32	GM METERS
STROKE POWER	=	115	GM METERS/SEC
T.P.R.	=	2673	DYNES-SEC/CM^5
TOTAL CYCLE LENGTH	=	282	MSEC
EJECTION TIME	=	106	MSEC
PERIOD OF IVC	=	35	MSEC

The key derived variable in determining the heart geometry quantities is the *internal volume* which is estimated based on the assumptions that:

(1) the left ventricle may be approximated by an ellipsoid of revolution (11), and

(2) the axis ratio may be assumed constant and approximately equal to the mean value between end-ejection and end-diastole.

Experimentally, Kraft-Hunter et al (12), Koushanpour and Collings (13), and others have shown that these assumptions are satisfactory based on the correlation between instantaneous volume using dye dilution, and biplane angiographic techniques and volume based on midplane radius. Of course, once the instantaneous volume is known, the determination of the other heart geometrical quantities becomes obvious.

Wall force refers to the total force acting on the midplane of the heart wall in the meridional direction and tending to separate it into halves. It is simply the product of the left ventricular pressure and the internal cross-sectional area of the heart in the plane of diameter measurement.

Two components of *wall stress,* average meridional and average circumferential, are calculated when both the internal and external diameters are measured. These formulae, as discussed by Walker et al (14), give the average wall stresses, taking into account the finite wall thickness and the non-spherical shape of the ventricle.

The *pressure* quantities, gradient and pulse pressure, are simply the algebraic differences between the denoted pressures located by the pattern recognition algorithms. The mean aortic pressure is obtained by summing the digitized values of aortic pressure between successive end-diastoles and dividing by the total number of points.

The *contraction velocities* at the equator are determined as discussed by Walker et al (14). The most important, contractile element velocity (an index of contractility), is calculated in two ways. The first method utilizes the circumferential wall stress and stems directly from the Hill model of an isolated muscle preparation. The other method recently introduced into the literature is direct analog measurement of dLnP/dt (10) which mathematically is equivalent to the first method provided the wall stress is sufficiently large and the rate of change of cardiac dimensions is small.*

*Mathematically, during the period of isometric (isovolumic) contraction,

$$V_{CE} = \frac{d\sigma/dt}{K(\sigma + C)} \quad \text{where } \sigma = \frac{Pr}{2H}$$

By making the assumption of slowly varying dimensions, this equation may be rewritten

$$V_{CE} = \frac{r}{2H} \frac{dP/dt}{[K(\frac{r}{2H} P + C)]}$$

or

$$V_{CE} = \frac{dP/dt}{[K(P + \frac{2H}{r} C)]} \cong \frac{1}{K} \frac{d \text{ Ln } P}{dt} \text{ when } \frac{2HC}{Pr} << 1$$

The energy quantity, *stroke work*, is calculated differently from the surrogate variable conventionally used in the cardiovascular literature, i.e., mean aortic pressure times the stroke volume. Since instantaneous pressures and volumes are known throughout a cycle, the purely physical definition of work, $\int PdV$, is used.

Stroke power as used in the cardiovascular literature is the average power over the period of ejection and it is simply determined by dividing the stroke work by the ejection time.

Peripheral resistance is defined as the difference between the mean aortic pressure and the end diastolic pressure in millimeters of mercury divided by the cardiac output in cc/sec times 1328. (The factor 1328 serves to convert blood pressure units (mm Hg) into absolute units of resistance, and is derived by multiplying the acceleration of gravity, G (980.6 cm sec^{-2}), by the weight of 1 mm Hg (1.3546 at 20°C), this product yielding dynes/cm^2 which when divided by cc/sec yields dyne sec cm^{-5}).

When the aorta is constricted by artificial means, two values of peripheral resistance are calculated based on aortic pressure distal and proximal to the constriction.

DATA ANALYSIS

Several Hewlett-Packard data analysis programs useful in cardiac data analysis are presently retrievable as Fortran subroutines in user programs.

These programs are being revised to serve as individual programs to analyze, upon instruction of the investigator, the data base created by the modular programs which define and address the individual cardiac cycle and compute the derived variables. In the latter mode, the investigator is simply required to enter on the graphics terminal the file name (dog #), the date of the experiment, the number of the record, the number of cycles to be analyzed within the record, the variables to be analyzed, and of course, the name of the data analysis routines. Generally, these programs may be classified as follows:

(a) auto-correlation and spectral density function

(b) cross correlation function

(c) linear and non-linear regression

(d) general statistics for single and multiple groups (mean, variance, standard deviation, confidence interval, histogram)

(e) probability function (Gaussian, Student's t, Poisson, etc.)

(f) multiple correlation (cross-product matrix, variance co-variance matrix, correlation matrix, mean and standard deviation)

(g) tests of hypothesis (Duncan's multiple range test, paired-t-test, variance and mean).

On a similar basis, several subroutines for data manipulation such as matrix inversion and ordering of an array, and data display routines such as cross, three dimensional, and histogram plotters are being modified.

SUMMARY

Large quantities of data are generated rapidly from experiments requiring several chronically implanted transducers and continuous measurements. For effective and efficient utilization of these data, an appropriately designed processing system is necessary. This paper describes the system hardware and program design considerations for acquisition, storage, reduction, and analysis of a typical set of cardiovascular variables. The system is based on a digital processor and contains provisions for on-line sampling and digitizing of analog signals, with real-time printout of results, and for filing and retrieval to permit off-line manipulation of selected variables. The major factors to be considered and modified in the course of system development are the storage and retrieval capacity of core or peripheral memory; the extent to which data can be analyzed while the experiment is in progress; the capability for a "quick look" at results as a basis for real-time modification of experimental procedures; and the simplicity and flexibility with which data can be retrieved from files, manipulated and edited by data analysis routines, and displayed or printed out for the investigator. Pro-

cedures for cycle definition and examples of data analysis are included in the description.

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52. DISCUSSION OF SECTION IV, SIGNAL CONDITIONING AND PROCESSING

Panel: Drs. Edward W. Hawthorne (Chairman), Joseph C. Greenfield, Jr., Carl F. Rothe, and Reddy R. V. Reddy.

TOPIC 1: Signal Conditioning

The discussants felt that telemetry systems are very expensive, less reliable and require more equipment than directly-coupled systems. Therefore, the decision to use telemetry should be made with considerable caution. Three major indications for telemetry were identified: (1) the general area of behavioral studies, (2) studies of free-roaming animals, and (3) studies which require use of non-docile animals such as the baboon. Both backpack and implant telemetry have been used successfully in primates. Baboons occasionally fall so that the backpack must be well-padded to protect the circuitry from physical damage. Chimpanzees tamper with a backpack but baboons will not.

The electronic technology for implantable telemetry systems was not felt to be particularly difficult. Power can be conserved by using magnetic switches which can be turned on and off from the outside and have proven reliability. The major problem lies in the extreme care which must be taken in assembly and packaging. The units must be scrupulously clean and hermetically sealed, since the primary cause of failure is leakage of body fluids into the circuitry. The attachment of a silastic-covered Dacron mesh permits these units to be easily sutured to internal sites.

Calibration of telemetered signals received considerable discussion. In particular, the determination of zero pressure baseline was considered since the available pressure transducers have an acceptable zero stability for only a few days. Direct transducer-manometer calibration at the end of the crucial part of an experiment was felt to be the best procedure for obtaining reliable values. This can be done by recapturing the animals by tranquilization and releasing them for continued monitoring after the calibration procedure. Values in free-roaming baboons were checked about every two weeks.

Since relatively large changes in blood pressure are generally of interest

in these situations, errors caused by shifts in barometric pressure are a minor problem, on the order of 2 or 3 mmHg. Flow calibration requires a procedure similar to that for pressure. Determination of cardiac output using an indicator dilution procedure can be used to verify calibration of the aortic probe. If in vitro calibrations are used, they must be done both before and after the experiment to check stability and reproducibility. At the end of the study the vessel can be cannulated and direct determinations of flow made. The ultrasonic Doppler flowmeters can be checked by using a signal generator to obtain appropriate sinusoidal frequencies which are processed by the receiver. This frequency-velocity correlation is determined by bench tests prior to the implantation.

The commercial versions of some instruments have caused problems. The redesign of developmental models to save money in manufacturing has occasionally led to the marketing of equipment with characteristics quite different from those described in original reports. Since there is no effective way to control this problem, users must carefully evaluate their instrument before beginning a series of experiments.

TOPIC 2: Signal Processing

A major concern of a future meeting might be what to do with data processing. There was general agreement that an essential step in information processing was to record the data on a good analog tape recorder. A certain amount of noise will be added by the tape, but the best currently available machines have a 45 to 50 db signal-to-noise ratio. Compromise with quality is particularly poor economy in the use of analog recording equipment. It makes no sense to put thousands of dollars of instrumentation into an animal and then use a cheap tape recorder.

The discussion then progressed to signal processing using analog computational techniques. These are frequently easier, better understood, and more economical of professional time than are the corresponding digital techniques. An additional virtue of analog signal processing is the inherent display flexibility and versatility. Analog processing is frequently easier to modify than is a digital computer program. Analog pre-processing of data is extremely useful when combined with digital techniques. Differentiation with respect to time is one of the most commonly performed operations and received considerable emphasis. The procedure for either analog or digital calculation of derivatives must be very carefully designed and tested. The end-result is always a compromise between smoothing the signal to decrease the noise, and distorting the data. Digital differentiation requires a 1 msec sample rate or less for reasonable accuracy. A suggested test for the

adequacy of a digital differentiator was to process a sine wave with an added random noise level of 5% of the signal amplitude. In the presence of noise, a 5 to 9 point moving quadratic fit to data sampled at 0.5 to 1 msec intervals gives satisfactory results. A triangular wave is useful for calibrating derivative techniques but is not an adequate test of the upper limit of frequency response. However, the degree to which the differentiator approaches a square wave output with a triangular wave input is a quick index of proper operation.

Analog computers are limited, however, for the multi-parameter analyses being conducted in most chronically instrumented animals. A dedicated small digital computer was felt to be necessary for the effective, rapid data analysis required by many current experiments. The proper sampling frequency for digital techniques was discussed. A 1 msec sampling rate might be ideal, but it may also "fill up" the computer after two or three heart beats. The users agreed that a 5 msec sampling rate was satisfactory for general purposes, especially if derivatives had been preprocessed.

There was considerable diversity of opinion regarding the degree of dedication required of a digital computer for a given individual investigator. The experiences to date with *time-shared* systems were *unsatisfactory*. The rapid reduction of computer costs will put a suitable system within the reach of many laboratories. Selection of a given system requires compromise between the complexity of the jobs to be performed and cost. One useful digital system was acquired for $10,000 and another was being rented for $22,000 a year. This cost is actually economical since laboratory productivity was increased and the computer is able to do the work of several technicians. Original costs of other systems ranged up to $100,000. Large scale digital computing should be done on a central facility.

The use of a combination of on-line and off-line processing was a common practice. On-line processing and associated immediate information feedback may be essential for some experiments. In other situations, the experimenter may need to print out the data file and mark it by hand, or replay the analog tape for intensive examination of a short interval of data which has particular interest. Although the noise level on a digital tape recorder might be lower than analog, digital recording was felt to be less essential.

A specific example of digital analysis receiving extended discussion was identification of ventricular end-diastolic pressure. It was concluded that digital computer algorithms for identifying specific events of the cardiac cycle, if carefully developed and evaluated, can be quite useful. Less automated procedures, such as direct data file display with subsequent manual identification of all points of interest, may be required in many instances.

A slightly different philosophy of the use of digital computation was also expressed. If relatively long time-constants are suitable for the physiological changes being studied, a digital computer may be very useful for data compression. Averaged values can be calculated on-line and the individual points discarded. There was concern that much data of physiological interest is really discontinuous, and that perhaps data from a few heart beats, taken at selected times, would be sufficient. The choice of analysis obviously depends on the hypotheses being examined.

Finally, it was recognized that a modern research facility which offers a wide range of experimental capabilities usually exceeds the expertise of an individual investigator, and a team becomes necessary. The individual investigator, however, still has an obligation to know the general characteristics and operating principles of his instrumentation and data processing systems.

SUMMARY

Considerable variation exists in the methods of conditioning and processing the signals obtained from the implanted transducers. Just as in the case of transducer selection and implantation, each investigator must choose and adapt the system most appropriate to his experimental design.

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tation.

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